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(54) Title: BASIC COMPOUNDS CONTAINING TERTIARY AMIDES WITH ACTIVITY ON TACHYKININ RECEPTORS, AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

(57) Abstract: Described herein are compounds having a base structure made up of an alkene or an aromatic group to which are bound two substituted vicinal amides containing one or more nitrogen atoms with basic characteristic and their pharmaceutically accepetable salts useful for the treatment of diseases that require the use of NK2 antagonists.

WO 02/20437 A2

BASIC COMPOUNDS CONTAINING TERTIARY AMIDES WITH ACTIVITY ON TACHYKININ RECEPTORS, AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

Field of the invention

The present invention relates to compounds having a base structure made up of an alkene or an aromatic group to which are bound two substituted vicinal amides containing one or more nitrogen atoms with basic characteristics, and to their pharmaceutically acceptable salts. Said compounds present activity on the tachykinin receptors and, in particular, are useful for the treatment of diseases that require the use of NK2 antagonists. The invention further relates to pharmaceutical compositions containing the aforesaid products as active principle.

State of the art

In the literature there are known many compounds having activity on tachykinin receptors in general, and as antagonists in particular. In many cases these compounds present structures of a peptide or pseudo-peptide type.

Amongst tachykinin receptors, the one known as NK2 is widely expressed in the peripheral nervous system of mammals. One of the various effects produced by selective stimulation of the NK2 receptor is the contraction of smooth muscle. Consequently, antagonists of the NK2 receptor can be considered agents capable of controlling the excessive contraction of smooth muscle in any pathological condition in which the release of tachykinins concurs with the genesis of the corresponding disorder.

Tachykinins have been implicated in numerous diseases including: asthma, allergic rhinitis, chronic obstructive pulmonary disease, cough, urticaria, inflammation (including inflammation of a neurogenic origin), pain (including neuropathic, visceral and ocular pain), hemicrania, rheumatoid arthritis, premenstrual tension, emesis (including emesis resistant to ondansetron), oedema, gastric hypermotility, diseases due to oesophageal reflux, Crohn's disease, problems due to gastric evacuation, ulcerous colitis, the irritable-colon syndrome, hypermotility of the detrusor, urinary incontinence, cystitis, and renal colics.

In particular, the bronchospastic component of asthma, cough, pulmonary irritations, intestinal spasms (for example, in Crohn's disease, in ulcerous colitis or

the irritable-colon syndrome), or local spasms of the bladder and of the ureter during cystitis, renal infections and colics can be considered conditions in which the administration of NK2 antagonists may be effective.

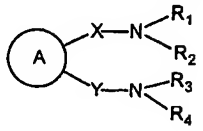
Examples of reviews that hypothesize the use of tachykinin antagonists in many of the diseases referred to above are: McLean S. (1996) Med. Res. Rev. 16, 297-317; Holzer P. (1998) Digestion 59(4), 269-83; Maggi C.A. (1997) Pharmacological Research 36(2), 153-69; von Sprecher *et al.* (1998) Drugs, 1(1), 73-91.

Peptide or pseudopeptides, either cyclic or linear, are known in the literature for having high antagonistic activity to the NK2 receptor of tachykinins.

Also known are many basic compounds containing a substituted aromatic amide and for which there is claimed an activity on the NK1 or NK2 receptor or both, such as those described in EP474561 and WO9410146. The structural characteristics of all these compounds are always considerably different from those that characterize the ones that form the subject of the present invention.

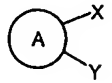
Summary of the invention

The present invention relates to products having the general formula (I)



(I)

in which the group



is made up of:

a C_{2-12} alkenyl group or an aromatic group in which the two substituents X and Y are bound to two adjacent carbon atoms;

- X and Y, which are the same as or different from one another, represent a -CO- or else -SO_2- group;

- R_1 and R_3, which are the same as or different from one another, represent a -C_{2-5}alkylidene-T-Ar_1 group in which T is a bond or a group chosen from among S, SO or SO_2, and Ar_1 is an aromatic group chosen from among benzene, pyridine, pyrimidine, pyrazine, pyridazine, pyrrole, furan, thiophene, triazole, imidazole, oxazole, thiazole, isoxazole, naphthalene, quinoline, isoquinoline, quinazoline, quinoxaline, cinnoline, phthalazine, indole, isoindole, benzofuran, isobenzofuran, benzothiophene, isobenzothiophene, benzotriazole, benzoimidazole, benzoxazole, benzothiazole, benzoisoxazole, and azulene, possibly substituted with one or two groups chosen from among fluoro-, chloro-, bromo-, nitro-, cyano-, hydroxy-, methoxy-, methyl-, trifluoromethyl-, trifluoromethoxy-, amino-, methylamino-, dimethylamino-, acetylamino-, mesylamino-, tosylamino-, tosyloxy-, carboxy-, carboxyamido-, guanidino-, and sulphamido-;

- R_2 and R_4, which are the same as or different from one another, represent a group chosen from among H, -C_{1-5}alkyl, -C_{1-5}alkylidene-NR_5R_6, in which :

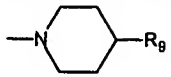
R_5 and R_6, which are the same as or different from one another, represent an H, -C_{1-5}alkyl, -C_{2-5}alkylidene-Q group, in which Q is a group chosen from between OR_7 and NR_7R_8 and in which R_7 and R_8, which are the same as or different from one another, represent an H, -C_{1-5}alkyl group; or NR_7R_8 together represent a group chosen from among piperidine, morpholine, pyrrolidine, thiomorpholine, thiomorpholin-1-oxide, thiomorpholin-1,1-dioxide piperazine, *N*-methyl-piperazine, and aziridine,

or else NR_5R_6 together represent a group chosen from among:

a) pyrrolidine, morpholine, thiomorpholine, thiomorpholin-1-oxide, thiomorpholin-1,1-dioxide, guanidine, guanidine mono-substituted or di-substituted with -C_{1-5}alkyl or -C_{1-5}acyl, -NH-CH=NH groups,

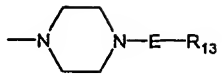
-NH-C(R_{12})=NH, where R_{12} is a -C_{1-5} alkyl group;

b) a 4-piperidone ethylene ketal group or else a piperidine of the type



in which R_9 is chosen from among H, -C_{1-5}alkyl, benzyl, OR_{10}, $NR_{10}R_{11}$, and in which R_{10} and R_{11}, which are the same as or different from one another, represent an H, -C_{1-5}alkyl group, or else $NR_{10}R_{11}$ together represent a group chosen from among piperidine, morpholine, pyrrolidine, thiomorpholine, thiomorpholin-1-oxide, thiomorpholin-1,1-dioxide, piperazine, *N*-methyl-piperazine, and aziridine;

c) a piperazine of the type



in which E represents a bond or else a group chosen from among -CO-, -SO_2-, -CONH-,

-SO_2NH- and R_{13} is a group chosen from among H, - C_{1-5} alkyl, -$(CH_2)_n$-adamantyl, -$(CH_2)_n$- Ar_2 in which n = 0,1,2 and Ar_2 is an aromatic group chosen from between naphthalene and benzene possibly substituted with 1, 2, 3 groups chosen from among F, Cl, CF_3, OH, OCH_3, $SOCH_3$, OCF_3, CN, C_{1-5}alkyl;

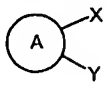
with the limitation that at least one between R_2 and R_4 must always be a -C_{1-5}alkylidene-NR_5R_6 group, as defined above,

understood both as individual stereoisomers, including those due to atropoisomery, and as mixtures in the racemic or non-racemic form, and their pharmaceutically acceptable salts.

Detailed description of the invention

The present invention enables the aforesaid problems to be overcome thanks to products of formula (I), as previously defined.

Preferably according to the invention the group



is made up of:

a) an olefin chosen from among:

in which Z and W, which are the same as or different from one another, represent an H, C_{1-5} alkyl group, or else together represent a C_{2-6} alkylidene group;

b) an aromatic group Ar, either mono-cyclic or bi-cyclic, in which the substituents X and Y are in an ortho position with respect to one another, the said group being chosen in the group made up of: benzene, pyridine, pyrimidine, pyrazine, pyridazine, pyrrole, furan, thiophene, triazole, imidazole, oxazole, thiazole,

isoxazole, naphthalene, quinoline, isoquinoline, quinazoline, quinoxaline, cinnoline, phthalazine, indole, isoindole, benzofuran, isobenzofuran, benzothiophene, isobenzothiophene, benzotriazole, benzoimidazole, benzoxazole, benzothiazole, and benzoisoxazole,

said aromatic group being possibly further substituted with one, two, three or four groups, which are the same as or different from one another, chosen in the group made up of: fluoro-, chloro-, bromo-, nitro-, cyano-, hydroxy-, methoxy-, methyl-, trifluoromethyl-, trifluoromethoxy-, amino-, methylamino-, dimethylamino-, acetylamino-, mesylamino-, tosylamino-, tosyloxy-, carboxy-, carboxyamido-, guanidino-, and sulphamido-;

and the other substituents are as previously defined.

A selection of preferred compounds, having the general formula (I), are those in which:

- R_1 and R_3, which are the same as or different from one another, represent a -C_{2-5}alkylidene-T-Ar_1 group in which T is a bond or a group chosen from between S and SO, and Ar_1 is an aromatic group chosen from among benzene, naphthalene, quinoline, isoquinoline, quinazoline, quinoxaline, cinnoline, phthalazine, indole, isoindole, benzofuran, isobenzofuran, benzothiophene, isobenzothiophene, benzotriazole, benzoimidazole, benzoxazole, benzothiazole, and benzoisoxazole, possibly substituted with one or two groups chosen from among fluoro-, chloro-, cyano-, hydroxy-, methoxy-, methyl-, trifluoromethyl-, trifluoromethoxy-, amino-, acetylamino-, mesylamino-, tosylamino-, tosyloxy-, guanidino-, and sulphamido-;
- R_2 and R_4, which are the same as or different from one another, represent a group chosen from among H, -C_{1-5}alkyl, -C_{1-5}alkylidene-NR_5R_6 in which :

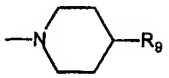
R_5 and R_6, which are the same as or different from one another, represent an H, -C_{1-5}alkyl, -C_{2-5}alkylidene-Q group, in which Q is a group chosen from between OR_7 and NR_7R_8 and in which R_7 and R_8, which are the same as or different from one another, represent an H, -C_{1-5}alkyl group; or NR_7R_8 together represent a group chosen from among piperidine, morpholine, pyrrolidine, thiomorpholine, thiomorpholin-1-oxide, thiomorpholin-1,1-dioxide, piperazine, and *N*-methyl-piperazine,

or else NR_5R_6 together represent a group chosen from among:

a) pyrrolidine, morpholine, thiomorpholine, thiomorpholin-1-oxide, thiomorpholin-1,1-dioxide, guanidine, guanidine mono-substituted or di- substituted with -C_{1-5}alkyl or -C_{1-5}acyl, -NH-CH=NH,

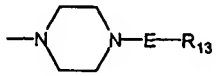
-NH-C(R_{12})=NH groups, where R_{12} is a -C_{1-5} alkyl group;

b) a 4-piperidone ethylene ketal group or else a piperidine of the type



in which R_9 is chosen from among H, -C_{1-5}alkyl, benzyl, OR_{10}, and $NR_{10}R_{11}$, and in which R_{10} and R_{11}, which are the same as or different from one another, represent an H, -C_{1-5}alkyl group, or else $NR_{10}R_{11}$ together represent a group chosen from among piperidine, morpholine, pyrrolidine, thiomorpholine, thiomorpholin-1-oxide, thiomorpholin-1,1-dioxide, piperazine, *N*-methyl-piperazine, and aziridine;

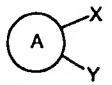
c) a piperazine of the type



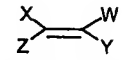
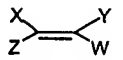
in which E represents a bond or else a group chosen from among -CO-, -SO_2-, -CONH-, -SO_2NH-, and R_{13} is a group chosen from among H, - C_{1-5} alkyl, -$(CH_2)_n$-adamantyl, -$(CH_2)_n$- Ar_2 in which n = 0,1,2 and Ar_2 is an aromatic group chosen from between naphthalene and benzene possibly substituted with 1, 2, 3 groups chosen from among F, Cl, CF_3, OH, OCH_3, $SOCH_3$, OCF_3, CN, and C_{1-5}alkyl;

with the limitation that at least one between R_2 and R_4 must always be a -C_{1-5}alkylidene-NR_5R_6 group as defined above, and the other substituents are as defined above.

A first particular selection of further preferred compounds are those of the general formula (I) in which the group:



may be an olefin chosen from between

 and 

in which Z and W, which are the same as or different from one another, represent an H, C_{1-5} alkyl group, or else together represent a C_{2-6} alkylidene, and the other substituents have the meanings previously defined.

To be considered as preferred compounds of the present solution are those in which the -C_{2-6}alkylidene part of Z and W is chosen from among -$(CH_2)_3$-, -$(CH_2)_4$-, -$(CH_2)_5$-, -$(CH_2)_6$-; the -C_{2-5}alkylidene part of R_1 and R_3 is chosen among -$(CH_2)_2$-, -$(CH_2)_3$-, -$(CH_2)_4$-, isopropylidene, isobutylidene; the -C_{1-5}alkylidene part in R_2 and R_4 is chosen from among -CH_2-, -$(CH_2)_2$-, -$(CH_2)_3$-, -$(CH_2)_4$-, isopropylidene;

-C_{1-5}alkyl is chosen from among methyl, ethyl, propyl, isopropyl, butyl, *ter*-butyl; and -C_{1-5}acyl is chosen from among formyl, acetyl, propanoyl, and isopropanoyl.

Particularly preferred are to be considered the compounds in which:

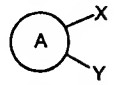
Z and W, which are the same as or different from one another, are H or methyl or together represent a butylidene group, and X and Y represent a -CO- group.

According to this first selection, as defined above, the following compounds are absolutely preferred:

-*cis*-but-2-enedioic acid *bis*-[[2-(3,4-dichloro-phenyl)-ethyl]-(3-morpholin-4-yl-propyl)-amide], and

- cyclohex-1-ene-1,2-dicarboxylic acid *bis*-[[2-(1H-indol-3-yl)-ethyl]-(2-morpholin-4-yl-ethyl)-amide].

A second particular selection of preferred compounds is represented by those of the general formula (I) , in which the group:



is an aromatic group Ar, either mono-cyclic or bi-cyclic, with the substituents X and Y in an ortho position with respect to one another,

chosen from among benzene, pyridine, pyrimidine, pyrazine, pyridazine, pyrrole, furan, thiophene, triazole, imidazole, oxazole, thiazole, isoxazole, naphthalene, quinoline, isoquinoline, quinazoline, quinoxaline, cinnoline, phthalazine, indole, isoindole, benzofuran, isobenzofuran, benzothiophene, isobenzothiophene,

benzotriazole, benzoimidazole, benzoxazole, benzothiazole, and benzoisoxazole, possibly further substituted with one, two, three or four groups, which are the same as or different from one another, chosen from among fluoro-, chloro-, bromo-, nitro-, cyano-, hydroxy-, methoxy-, methyl-, trifluoromethyl-, trifluoromethoxy-, amino-, methylamino-, dimethylamino-, acetylamino-, mesylamino-, tosylamino-, tosyloxy-, carboxy-, carboxyamido-, guanidino-, and sulphamido-, and the other substituents are as previously defined.

To be considered as particularly preferred compounds are compounds in which :

- the aromatic group Ar is chosen in the group made up of: benzene, pyridine, pyrazine, pyrimidine, naphthalene, quinoline, quinazoline, quinoxaline, cinnoline, phthalazine, indole, benzofuran, benzothiophene, benzothiazole, and benzoisoxazole, and is possibly further substituted with one, two, three or four groups, which are the same as or different from one another, chosen from among: fluoro-, chloro-, nitro-, hydroxy-, methoxy-, methyl-, trifluoromethyl-, trifluoromethoxy-, amino-, mesylamino-, and guanidino.

To be considered as even more preferred are those in which:

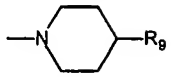
- the aromatic group Ar is chosen in the group made up of benzene, naphthalene, pyrazine, and pyridine possibly further substituted with one, two, three or four groups, which are the same as or different from one another, chosen from among : fluoro-, chloro-, nitro-, amino-, hydroxy-, mesylamino-, and tosyloxy-;
- R_1 and R_3, which are the same as or different from one another, represent a $-C_{2\text{-}5}$alkylidene-T-Ar_1 group in which T is a bond or a group chosen from between S and SO, and Ar_1 is an aromatic group chosen from among benzene, naphthalene, quinoline, indole, benzofuran, benzothiophene, benzoxazole, and benzothiazole, possibly substituted with one or two groups chosen from among fluoro-, chloro-, cyano-, hydroxy-, methoxy-, methyl-, trifluoromethyl-, trifluoromethoxy-, amino-, acetylamino-, mesylamino-, and guanidino-;
- R_2 and R_4, which are the same as or different from one another, represent a group chosen from among H, $-C_{1\text{-}5}$alkyl, $-C_{1\text{-}5}$alkylidene-NR_5R_6 in which :
  R_5 and R_6, which are the same as or different from one another, represent an H, $-C_{1\text{-}5}$alkyl, $-C_{2\text{-}5}$alkylidene-Q group in which Q is an OR_7 group and in which R_7 represents an H, $-C_{1\text{-}5}$alkyl group,

or else NR_5R_6 together represent a group chosen from among:

a) pyrrolidine, morpholine, thiomorpholine, thiomorpholin-1-oxide, thiomorpholin-1,1-dioxide, guanidine, guanidine mono-substituted or di-substituted with $-C_{1\text{-}5}$alkyl or $-C_{1\text{-}5}$acyl, -NH-CH=NH,

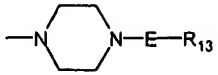
-NH-C(R_{12})=NH groups, where R_{12} is a $-C_{1\text{-}5}$ alkyl group;

b) a 4-piperidon ethylene ketal group or else a piperidine of the type



in which R_9 is chosen from among H, OH, piperidine, morpholine, thiomorpholine, thiomorpholin-1-oxide, thiomorpholin-1,1-dioxide;

c) a piperazine of the type



in which E represents a bond or else a group chosen from between -CO- and -CONH-, and R_{13} is a group chosen from among H, $-C_{1\text{-}5}$ alkyl, $-(CH_2)_n$-adamantyl, $-(CH_2)_n$-Ar_2 in which n = 0,1,2 and Ar_2 is a benzene possibly substituted with 1, 2, 3 groups chosen from among F, Cl, CF_3, OH, OCH_3, $SOCH_3$, OCF_3, CN, $C_{1\text{-}5}$alkyl

- the $-C_{2\text{-}5}$alkylidene part of R_1 and R_3 is chosen in the $-(CH_2)_2$-, $-(CH_2)_3$-, $-(CH_2)_4$-, isopropylidene, isobutylidene group; the $-C_{1\text{-}5}$alkylidene part in R_2 and R_4 is chosen from among $-CH_2$-, $-(CH_2)_2$-, $-(CH_2)_3$-, $-(CH_2)_4$-, isopropylidene; $-C_{1\text{-}5}$alkyl is chosen from among methyl, ethyl, propyl, isopropyl, butyl, *ter*-butyl; and $-C_{1\text{-}5}$acyl is chosen from among formyl, acetyl, propanoyl, isopropanoyl.

Finally, as absolutely preferred compounds, according to this second selection as defined above, the following compounds are to be considered:

N,N'-bis-[2-(1H-indol-3-yl)-ethyl]-*N*-methyl-*N'*-(2-[4-(3-nitro-phenylcarbamoyl)-piperazin-1-yl]-ethyl)-phthalamide;

N-[2-[4-(2-*tert*-butyl-phenylcarbamoyl)-piperazin-1-yl]-ethyl)-*N,N'-bis*-[2-(1H-indol-3-yl)-ethyl]-*N'*-methyl-phthalamide;

N-[2-(4-benzyl-piperazin-1-yl)-ethyl]-*N,N'-bis*-[2-(1H-indol-3-yl)-ethyl]-*N'*-methyl-phthalamide;

N-[2-(4-benzylcarbamoyl-piperazin-1-yl)-ethyl]-*N,N'-bis*-[2-(1H-indol-3-yl)-ethyl]-*N'*-

methyl-phthalamide;

N-[2-(4-benzyl-piperazin-1-yl)-ethyl]-*N*-[2-(1H-indol-3-yl)-ethyl]-*N'*-(2-morpholin-4-yl-ethyl)-*N'*-(2-naphthalene-2-yl-ethyl)-phthalamide;

N-[3-(4-benzyl-piperazin-1-yl)-propyl]-*N,N'-bis*-[2-(1H-indol-3-yl)-ethyl]-*N'*-methyl-phthalamide;

N,N'-bis-[2-(1H-indol-3-yl)-ethyl]-*N*-methyl-*N'*-2-[4-(4-trifluoromethoxy-phenylcarbamoyl)-piperazin-1-yl]-ethyl}-phthalamide;

N,N'-bis-[2-(1H-indol-3-yl)-ethyl]-*N*-methyl-*N'*-[2-(4-phenylcarbamoyl-piperazin-1-yl)-ethyl]-phthalamide;

N-[2-[4-(3,4-dichloro-phenylcarbamoyl)-piperazin-1-yl]-ethyl]-*N,N'-bis*-[2-(1H-indol-3-yl)-ethyl]-*N'*-methyl-phthalamide;

cis-but-2-enedioic acid *bis*-[[2-(3,4-dichloro-phenyl)-ethyl]-(3-morpholin-4-yl-propyl)-amide]

Naphthalene-2,3-dicarboxylic acid *bis*-[[2-(1H-indol-3-yl)-ethyl]-(2-morpholin-4-yl-ethyl)-amide];

Naphthalene-2,3-dicarboxylic acid *bis*-[[2-(5-fluoro-1H-indol-3-yl)-ethyl]-(3-morpholin-4-yl-propyl)-amide];

Cyclohex-1-ene-1,2-dicarboxylic acid *bis*-[[2-(1H-indol-3-yl)-ethyl]-(2-morpholin-4-yl-ethyl)-amide]

Pyrazin-2,3-dicarboxylic acid 2-[[2-(3,4-dichloro-phenyl)-ethyl]-(3-morpholin-4-yl-propyl)-amide] 3-[[2-(1H-indol-3-yl)-ethyl]-(3-morpholin-4-yl-propyl)-amide];

Pyrazin-2,3-dicarboxylic acid 2-[[2-(3,4-dichloro-phenyl)-ethyl]-(3-morpholin-4-yl-propyl)-amide] 3-[[2-(1H-indol-3-yl)-ethyl]-amide);

N^1,N^2-*bis*-[2-(1H-indol-3-yl)-ethyl]-N^1,N^2-*bis*-(3-morpholin-4-yl-propyl)-4-nitro-phthalamide;

Naphthalene-1,2-dicarboxylic acid *bis*-[[2-(3,4-dichloro-phenyl)-ethyl]-(3-morpholin-4-yl-propyl)-amide];

N^1,N^2-*bis*-[2-(1H-indol-3-yl)-ethyl N^1,N^2-*bis*-(2-morpholin-4-yl-ethyl)-4-nitro-phthalamide;

N^1,N^2-*bis*-[2-(1H-indol-3-yl)-ethyl]-N^1,N^2-*bis*-(3-morpholin-4-yl-propyl)-3-nitro-phthalamide;

N^1,N^2-*bis*-[2-(3,4-dichloro-phenyl)-ethyl]-4-hydroxy-N^1,N^2-*bis*-(3-morpholin-4-yl-propyl)-phthalamide;

4-Hydroxy-N^1,N^2-*bis*-[2-(1H-indol-3-yl)-ethyl]-N^1,N^2-*bis*-(3-morpholin-4-yl-propyl)-phthalamide;

N^1,N^2-*bis*-[2-(3,4-dichloro-phenyl)-ethyl]-N^1,N^2-*bis*-(3-morpholin-4-yl-propyl)-4-nitro-phthalamide;

Pyridin-3,4-dicarboxylic acid *bis*-[[2-(3,4-dichloro-phenyl)-ethyl]-(3-morpholin-4-yl-propyl)-amide];

4-amino-N^1,N^2-*bis*-[2-(1H-indol-3-yl)-ethyl]-N^1,N^2-*bis*-(3-morpholin-4-yl-propyl)-phthalamide;

N^1,N^2-*bis*-[2-(1H-indol-3-yl)-ethyl]-4-methanesulphonylamino-N^1,N^2-*bis*-(3-morpholin-4-yl-propyl)-phthalamide;

Toluene-4-sulphonic acid 3,4-*bis*-[[2-(1H-indol-3-yl)-ethyl]-(3-morpholin-4-yl-propyl)-carbamoyl]-phenyl ester;

benzene-1,2-disulphonic acid *bis*-[[2-(1H-indol-3-yl)-ethyl]-(3-morpholin-4-yl-propyl)-amide];

Benzene-1,2-disulphonic acid *bis*-[[2-(1H-indol-3-yl)-ethyl]-(2-morpholin-4-yl-ethyl)-amide];

N,N'-*bis*-[2-(1H-indol-3-yl)-ethyl *N,N'*-*bis*-(3-morpholin-4-yl-propyl)-phthalamide;

N,N'-*bis*-[2-(3,4-dichloro-phenyl)-ethyl *N,N'*-*bis*-(3-morpholin-4-yl-propyl)-phthalamide;

N-[2-(1H-*indo*l-3-yl)-ethyl]-*N*-methyl-*N'*-(2-morpholin-4-yl-ethyl)-*N'*-(2-naphthalene-2-yl-ethyl)-phthalamide;

N,N'-bis-[2-(3,4-dichloro-phenyl)-ethyl]-*N,N'-bis*-(2-morpholin-4-yl-ethyl)-phthalamide;

N,N'-bis-[2-(1H-indol-3-yl)-ethyl]-*N*-methyl-*N'*-(3-thiomorpholin-4-yl-propyl)-phthalamide;

N,N'-bis-[2-(1H-indol-3-yl)-ethyl]-*N,N'-bis*-(3-thiomorpholin-4-yl-propyl)-phthalamide;

N-(2-[1,4']bipiperidinyl-1'-yl-ethyl)-*N,N'-bis*-[2-(1H-indol-3-yl)-ethyl]-*N'*-methyl-phthalamide;

N,N'-bis-(3-[1,4']bipiperidinyl-1'-yl-propyl)-*N,N'-bis*-[2-(1H-indol-3-yl)-ethyl]-phthalamide;

N,N'-bis-(2-morpholin-4-yl-ethyl *N,N'-bis*-(2-naphthalene-2-yl-ethyl)-phthalamide;
N,N'-bis-[2-(1H-indol-3-yl)-ethyl *N,N'-bis*-(2-morpholin-4-yl-ethyl)-phthalamide;
N-[2-(1H-*ind*ol-3-yl)-ethyl]-*N,N'-bis*-(2-morpholin-4-yl-ethyl)-*N'*-(2-naphthalene-2-yl-ethyl)-phthalamide;
N,N'-bis-[2-(5-fluoro-1H-indol-3-yl)-ethyl]-*N,N'-bis*-(3-morpholin-4-yl-propyl)-phthalamide;
N,N'-bis-[2-(1H-indol-3-yl)-ethyl]-*N*-methyl-*N'*-(3-morpholin-4-yl-propyl)-phthalamide;
N,N'-bis-[2-{*bis*-(2-methoxy-ethyl)-amino]-ethyl}- *N,N'-bis*-[2-(1H-indol-3-yl)-ethyl]-phthalamide;
N-(2-{4-[*N*-(2-*tert*-butyl-phenyl)-carbamimidoyl]-piperazin-1-yl}-ethyl)-*N,N'-bis*-[2-(1H-indol-3-yl)-ethyl]-*N'*-methyl-phthalamide;
N-(2-{4-[*N*-(2-*tert*-butyl-phenyl)-*N'*-methyl-carbamimidoyl]-piperazin-1-yl}-ethyl)-*N,N'-bis*-[2-(1H-indol-3-yl)-ethyl]-*N'*-methyl-phthalamide;
N-(2-{4-[*N*-(2-*tert*-butyl-phenyl)-*N'*-methyl-carbamimidoyl]-piperazin-1-yl}-ethyl)-*N'*-[2-(3,4-dichloro-phenyl)-ethyl]-*N*-[2-(1H-indol-3-yl)-ethyl]-*N'*-methyl-phthalamide;
N-[2-(3,4-dichloro-phenyl)-ethyl]-*N'*-[2-(1H-indol-3-yl)-ethyl]-*N*-methyl-*N'*-[2-(4-phenylacetyl-piperazin-1-yl)-ethyl]-phthalamide;
N,N'-bis-[2-(1H-indol-3-yl)-ethyl]-*N*-methyl-*N'*-(2-[4-(tricyclo[3.3.1.1^{0,0}]decane-1-carbonyl)-piperazin-1-yl]-ethyl)-phthalamide;
N,N'-bis-[2-(1H-indol-3-yl)-ethyl]-*N*-methyl-*N'*-{2-[4-(tricyclo[3.3.1.1^{0,0}]-dec-1-yl-acetyl)-piperazin-1-yl]-ethyl}-phthalamide;
N-[2-(4-acetyl-piperazin-1-yl)-ethyl]-*N,N'-bis*-[2-(1H-indol-3-yl)-ethyl]-*N'*-methyl-phthalamide;
N,N'-bis-[2-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-ethyl]-*N,N'-bis*-[2-(1H-indol-3-yl)-ethyl]-phthalamide;
N-[2-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-ethyl]-*N,N'-bis*-[2-(1H-indol-3-yl)-ethyl]-*N'*-methyl-phthalamide.
N-{2-[4-(Butane-1-sulfonyl)-piperazin-1-yl]-ethyl}-*N,N'*-bis-[2-(1*H*-indol-3-yl)-ethyl]-*N'*-methyl-phthalamide
N-[2-(4-Allylcarbamoyl-piperazin-1-yl)-ethyl]-*N,N'*-bis-[2-(1*H*-indol-3-yl)-ethyl]-*N'*-methyl-phthalamide

N,N'-Bis-[2-(1*H*-indol-3-yl)-ethyl]-*N*-methyl-*N'*-[2-(4-thiomorpholin-4-yl-methyl-piperidin-1-yl)-ethyl]-phthalamide
N,N'-Bis-[2-(1*H*-indol-3-yl)-ethyl]-*N*-methyl-*N'*-{2-[4-(4-nitro-benzenesulfonyl)-piperazin-1-yl]-ethyl}-phthalamide
N,N'-Bis-[2-(1*H*-indol-3-yl)-ethyl]-*N*-methyl-*N'*-[2-(4-phenylmethanesulfonyl-piperazin-1-yl)-ethyl]-phthalamide
N,N'-Bis-[2-(1*H*-indol-3-yl)-ethyl]-*N*-[2-(4-isopropyl-thiocarbamoyl-piperazin-1-yl)-ethyl]-*N'*-methyl-phthalamide
3-(4-{2-[[2-(*H*-Indol-3-yl)-ethyl]-(2-{[2-(*H*-indol-3-yl)-ethyl]-methyl-carbamoyl}-benzoyl)-amino]-ethyl}-piperazine-1-sulfonyl)-thiophene-2-carboxylic acid methyl ester
N,N'-Bis-[2-(1*H*-indol-3-yl)-ethyl]-*N*-methyl-*N'*-{2-[4-(thiophene-2-sulfonyl)-piperazin-1-yl]-ethyl}-phthalamide
N,N'-Bis-[2-(1*H*-indol-3-yl)-ethyl]-*N*-methyl-*N'*-{2-[4-(2-nitro-benzenesulfonyl)-piperazin-1-yl]-ethyl}-phthalamide
N-{2-[4-(Benzo[*b*]thiophene-2-carbonyl)-piperazin-1-yl]-ethyl}-*N,N'*-bis-[2-(1*H*-indol-3-yl)-ethyl]-*N'*-methyl-phthalamide
N-{2-[4-(3,5-Dimethyl-isoxazole-4-sulfonyl)-piperazin-1-yl]-ethyl}-*N,N'*-bis-[2-(1*H*-indol-3-yl)-ethyl]-*N'*-methyl-phthalamide
N-(2-{4-[*N*-(2-*tert*-Butyl-phenyl)-*N'*-furan-2-ylmethyl-carbamimidoyl]-piperazin-1-yl}-ethyl)-*N,N'*-bis-[2-(1*H*-indol-3-yl)-ethyl]-*N'*-methyl-phthalamide, acetic acid salt
N-(2-{4-[*N*-Furan-2-ylmethyl-*N'*-(2-methylsulfanyl-ethyl)-carbamimidoyl]-piperazin-1-yl}-ethyl)-*N,N'*-bis-[2-(1*H*-indol-3-yl)-ethyl]-*N'*-methyl-phthalamide, acetic acid salt
N-(2-Benzo[*b*]thiophen-3-yl-ethyl)-*N'*-[2-(4-benzyl-piperazin-1-yl)-ethyl]-*N'*-[2-(1*H*-indol-3-yl)-ethyl]-*N*-methyl-phthalamide
N-[2-(4-Benzyl-piperazin-1-yl)-ethyl]-*N*-[2-(1*H*-indol-3-yl)-ethyl]-*N'*-methyl-*N'*-[2-(4-nitro-phenyl)-ethyl]-phthalamide
N-[2-(4-Benzyl-piperazin-1-yl)-ethyl]-*N'*-(2-biphenyl-4-yl-ethyl)-*N*-[2-(1*H*-indol-3-yl)-ethyl]-*N'*-methyl-phthalamide

According to the present invention the pharmaceutically acceptable salts of the compounds of the general formula (I) are those formed therefrom with organic and inorganic acids chosen from the following group: hydrochloric acid, hydrobromic

acid, sulphuric acid, phosphoric acid, carbonic acid, acetic acid, trifluoroacetic acid, trichloroacetic acid, oxalic acid, malonic acid, malic acid, succinic acid, tartaric acid, citric acid, methanesulphonic acid, *p*-toluenesulphonic acid, maleic acid, and fumaric acid.

As may be seen from the formula and from the examples given above, the compounds that form the subject of the present invention are characterized in that they present a base structure made up of an olefin or of an aromatic group, to which are bound two substituted vicinal amides, preferably tertiary, each of which carries another aromatic group and, at least one of which carries one or more basic nitrogens.

It may moreover be noted that the compounds according to the invention present substantially simple structures; that preferably their molecular weight is less than 1000; and that they present, at the most, two stereogenic centres.

The compounds forming the subject of the present invention have proved active on tachykinin receptors, and consequently a use thereof is contemplated in pharmaceutical formulations for the treatment of diseases in which tachykinins are implicated.

These compounds are therefore viewed as valid alternatives to known compounds active on tachykinin receptors, and in particular on NK2 antagonists.

The compounds forming the subject of the present invention can be obtained by means of reactions of condensation between the pre-formed amines and the corresponding di-acids (or synthetic equivalent), using reagents and adopting experimental conditions as reported in the current specific literature and consequently well known to a person skilled in the art, for example according to the reaction schemes illustrated hereinafter by way of example as Procedure A and Procedure B.

Non-limiting examples of the present invention are the compounds described below.

The compounds were characterized using magnetic resonance techniques (data acquired at the temperature of 300°K, at 500 MHz in DMSO-d6) and mass spectrometry (with the ESI technique).

EXAMPLES

Procedure A (from anhydrides)

150 mg of phthalic anhydride (1.0 mmol) were added to a solution of an appropriate secondary amine B (1.0 mmol) in 30 ml of *N,N*-dimethylformamide. After stirring for 10 minutes, the following were added to the solution, in succession: 470 mg of bromotripyrrolidinephosphonium hexafluorophosphate (1.0 mmol), 1 mmol of an appropriate amine B1, and at least 2 mmol of triethylamine. After 12 hours of stirring at room temperature, followed by aqueous work-up, the residue deriving from the organic phase was purified by chromatography.

In this way, for example, the following compounds were obtained:

Example 1 - *N,N'-bis*-[2-(1H-indol-3-yl)-ethyl]-*N*-methyl-*N'*-[2-[4-(3-nitro-phenylcarbamoyl)-piperazin-1-yl]-ethyl]-phthalamide

(A = benzene, X = Y= CO, R_1= R_3= 2-(1H-indol-3-yl)-ethyl, R_2= methyl, R_4 = 2-[4-(3-nitro-phenylcarbamoyl)-piperazin-1-yl]-ethyl)

1H-NMR; c.s.(ppm): 2.15(m); 2.20(m); 2.39(t); 2.45(m); 2.58(t); 2.78(s); 2.83(s); 2.90-3.02(m); 3.00(s); 3.02(s); 3.20(t); 3.34-3.69(m); 6.80(m); 6.90-7.09(m); 7.15(d); 7.22(m); 7.27-7.53(m); 7.77(m); 7.88(m); 8.44-8.48(m); 8.93-8.99(m); 10.74-10.83(m).

MS; m/z = 741 (MH^+).

Example 2 - *N*-[2-[4-(2-*tert*-butyl-phenylcarbamoyl)-piperazin-1-yl]-ethyl]-*N,N'-bis*-[2-(1H-indol-3-yl)-ethyl]-*N'*-methyl-phthalamide

(A = benzene, X = Y= CO, R_1= R_3= 2-(1H-indol-3-yl)-ethyl, R_2= methyl, R_4 = 2-[4-(2-*tert*-butyl-phenylcarbamoyl)-piperazin-1-yl]-ethyl)

1H-NMR; c.s.(ppm): 1.27-1.39(m); 2.13(m); 2.38(t); 2.42-2.47(m); 2.77(s); 2.83(s); 2.91-3.02(m); 3.00(s); 3.03(s); 3.39-3.45(m); 3.58-3.70(m); 6.80(m); 6.86-7.09(m); 7.16(m); 7.22(m); 7.26-7.48(m); 7.62(dd); 7.77-7.84(m); 10.74-10.84(m).

MS; m/z = 752 (MH^+).

Example 3 - *N*-[2-(4-benzyl-piperazin-1-yl)-ethyl]-*N,N'-bis*-[2-(1H-indol-3-yl)-ethyl]-*N'*-methyl-phthalamide

(R_4 = 2-[4-benzyl-piperazin-1-yl]-ethyl, and the other substituents as in Example 1)

1H-NMR; c.s.(ppm): 2.11-2.46(m); 2.76(s); 2.82(s); 2.88-3.00(m); 2.98(s); 3.01(s); 3.13(t); 3.19(t); 3.38(m); 3.44(s); 3.53(b); 3.60-3.68(m); 6.78(m); 6.88-7.08(m); 7.12(d); 7.18-7.46(m); 7.59(d); 7.61(d); 10.72-10.81(m).

MS; m/z = 667 (MH^+).

Example 4 - *N*-[2-(4-benzylcarbamoyl-piperazin-1-yl)-ethyl]-*N*,*N*'-*bis*-[2-(1H-indol-3-yl)-ethyl]-*N*'-methyl-phthalamide

(R_4 = 2-(4-benzylcarbamoyl -piperazin-1-yl)-ethyl, and the other substituents as in Example 1)

1H-NMR; c.s.(ppm): 2.07(m); 2.12(m); 2.34-2.43(m); 2.47(m); 2.54m); 2.76(s); 2.82(s); 2.90-3.01(m); 2.99(s); 3.02(s); 3.16-3.24(m); 3.39(m); 3.54-3.69(m); 4.21(m); 6.79(m); 6.89-7.08(m); 7.13(d); 7.18-7.47(m); 7.61(m); 10.73-10.83(m).

MS; m/z = 710 (MH^+).

Example 5 - *N*-[2-(4-benzyl-piperazin-1-yl)-ethyl]-*N*-[2-(1H-indol-3-yl)-ethyl]-*N*'-(2-morpholin-4-yl-ethyl)-*N*'-(2-naphthalene-2-yl-ethyl)-phthalamide

(R_2 = 2-(4-benzyl-piperazin-1-yl)-ethyl, R_3 = 2-naphthalene-2-yl-ethyl, R_4 = 2-morpholin-4-yl-ethyl, and the other substituents as in Example 1)

1H-NMR; c.s.(ppm): 2.15-4.28(b); 6.75-6.83(m); 6.87-6.94(m); 6.97-7.10(m); 7.13(d); 7.22(b); 7.28-7.53(m); 7.61(d); 7.64(d); 7.74-7.90(m); 9.76(b); 10.77(b); 10.80(b); 10.85(b).

MS; m/z = 777 (MH^+).

Example 6 - *N*-[3-(4-benzyl-piperazin-1-yl)-propyl]-*N*,*N*'-*bis*-[2-(1H-indol-3-yl)-ethyl]-*N*'-methyl-phthalamide

(R_4 = 3-[4-benzyl-piperazin-1-yl]-propyl, and the other substituents as in Example 1)

1H-NMR ; c.s.(ppm): 1.57-1.76(m); 2.01-2.38(m); 2.76(s); 2.81-2.99(m); 2.82(s); 2.97(s); 3.00(s); 3.35(s); 3.44(s); 3.59-3.68(m); 6.79(m); 6.88-7.08(m,6H); 7.14-7.46(m,12H); 7.59(m,1H); 10.74-10.82(m,2H).

MS; m/z = 681 (MH^+).

Example 7 - *N*,*N*'-*bis*-[2-(1H-indol-3-yl)-ethyl]-*N*-methyl-*N*'-2-[4-(4-trifluoromethoxy-phenylcarbamoyl)-piperazin-1-yl]-ethyl)-phthalamide

(R_4 = 2-[4-(4-trifluoromethoxy-phenylcarbamoyl)-piperazin-1-yl]-ethyl, and the other substituents as in Example 1)

1H-NMR; c.s.(ppm): 2.13(m); 2.18(m); 2.38(t); 2.45(m); 2.57(t); 2.77(s); 2.83(s); 2.90-3.03(m); 3.00(s); 3.03(s); 3.19(t); 3.25(t); 3.42(m); 3.56-3.70(m); 6.80(m); 6.89-7.09(m); 7.15(d); 7.21(m); 7.30-7.50(m); 7.50-7.65 (m); 8.61(s); 8.63(s); 8.64(s); 8.676(s); 10.73-10.83(m).

MS; m/z = 780 (MH^+).

Example 8 - *N*,*N*'-*bis*-[2-(1H-indol-3-yl)-ethyl]-*N*-methyl-*N*'-[2-(4-phenylcarbamoyl-piperazin-1-yl)-ethyl]-phthalamide

(R_4 = 2-(4-phenylcarbamoyl-piperazin-1-yl)-ethyl, and the other substituents as in Example 1)

1H-NMR; c.s.(ppm): 2.13(m); 2.18(m); 2.38(t); 2.45(m); 2.57(t); 2.77(s); 2.83(s); 2.90-3.03(m); 3.00(s); 3.03(s); 3.19(t); 3.25(t); 3.42(m); 3.56-3.70(m); 6.80(m); 6.89-7.09(m); 7.15(d); 7.21(m); 7.27-7.48(m); 7.61(m); 8.41(s); 8.42(s); 8.44(s); 8.46(s); 10.73-10.83(m).

MS; m/z = 696 (MH^+).

Example 9 - *N*-[2-[4-(3,4-dichloro-phenylcarbamoyl)-piperazin-1-yl]-ethyl]-*N*,*N*'-*bis*-[2-(1H- indol-3-yl)-ethyl]-*N*'-methyl-phthalamide

(R_4 = 2-[4-(3,4-dichloro-phenylcarbamoyl)-piperazin-1-yl]-ethyl, and the other substituents as in Example 1)

1H-NMR; c.s.(ppm): 2.13(m); 2.18(m); 2.38(t); 2.42-2.47(m); 2.57(t); 2.77(s); 2.83(s); 2.91-3.02(m); 2.99(s); 3.03(s); 3.19(m); 3.25(m); 3.39-3.45(m); 3.56-3.69(m); 6.80(m); 6.90-7.09(m); 7.15(d); 7.21(m); 7.27-7.48(m); 7.61(m); 7.82(m); 8.71-8.76(m); 10.73-10.83(m).

MS; m/z = 764 (MH^+).

With a similar procedure the following compounds deriving from other appropriate symmetrical anhydrides were obtained:

Example 10 - *cis*-but-2-enedioic acid *bis*-[[2-(3,4-dichloro-phenyl)-ethyl]-(3-morpholin-4-yl-propyl)-amide]

(A = *cis*-but-2-ene, X = Y= CO, R_1= R_3= 2-(3,4-dichloro-phenyl)-ethyl, R_2= R_4 = 3-morpholin-4-yl-propyl)

1H-NMR; c.s.(ppm): 1.60(b,2H); 2.18(q); 2.22(t); 2.28(b); 2.76-2.85(m,2H); 3.18-3.25(m,2H); 3.47(m,2H); 3.54(b,4H); 6.33(s); 6.35(d); 6.49(d); 6.50(s); 7.23-7.27(m,1H); 7.50-7.57(m,2H).

MS; m/z = 713.5 (MH^+).

Example 11 - naphthalene-2,3-dicarboxylic acid *bis*-[[2-(1H-indol-3-yl)-ethyl]-(2-morpholin-4-yl-ethyl)-amide]

(A = naphthalene 2,3 di-substituted , X = Y= CO, R_1= R_3= 2-(1H-indol-3-yl)-ethyl R_2= R_4 = 2-morpholin-4-yl-ethyl)

1H-NMR; c.s.(ppm): 2.10(b); 2.14(b); 2.40-2.48(m); 2.58(m); 3.03(b); 3.18(d); 3.24(t); 3.37-3.46(m); 3.54(t); 3.60(t); 3.70(t); 6.40(t); 6.71(m); 6.87-7.10(m); 7.24(m); 7.35(m); 7.60-7.68(m); 7.79(s); 7.88-7.94(m); 8.01(d); 10.72(b); 10.74(b); 10.82(b); 10.84(b).

MS; m/z = 727 (MH^+).

Example 12 - naphthalene-2,3-dicarboxylic acid *bis*-[[2-(5-fluoro-1H-indol-3-yl)-ethyl]-(3-morpholin-4-yl-propyl)-amide]

(R_1= R_3= 2-(5- fluoro-1H-indol-3-yl)-ethyl, R_2= R_4 = 3-morpholin-4-yl-propyl, and the other substituents as in Example 11)

1H-NMR; c.s.(ppm): 1.93(b); 2.07(b); 2.88-3.88(m); 4.03(b); 6.55(d); 6.65(d); 6.76(m); 6.89-6.97(m); 7.06(s); 7.09(s); 7.22-7.44(m);7.59-7.67(m); 7.74(s); 7.80-7.99(m); 9.63(b); 9.79(b);10.86(b); 10.91(b); 10.98(b); 11.01(b).

MS; m/z = 791 (MH^+).

Example 13 - cyclohex-1-ene-1,2-dicarboxylic acid *bis*-[[2-(1H-indol-3-yl)-ethyl]-(2-morpholin-4-yl-ethyl)-amide]

(A = cyclohex-1-ene, X = Y= CO, R_1= R_3= 2-(1H-indol-3-yl)-ethyl, R_2= R_4 = 2-morpholin-4-yl-ethyl)

1H-NMR; c.s.(ppm): 1.84(b); 2.17(b); 2.22(b); 2.30-2.47(m); 2.84(q); 2.94(b); 3.43-3.56(m); 6.89(t); 6.94-7.15(m); 7.29-7.36(m,1H); 7.54(d); 7.58-7.65(m); 10.7-10.9(m,1H).

MS; m/z = 681 (MH^+).

Example 14 - pyrazin-2,3-dicarboxylic acid 2-[[2-(3,4-dichloro-phenyl)-ethyl]-(3-morpholin-4-yl-propyl)-amide] 3-[[2-(1H-indol-3-yl)-ethyl]-(3-morpholin-4-yl-propyl)-amide]

(A = pyrazin, X = Y= CO, R_1= 2-(1H-indol-3-yl)-ethyl, R_2= R_4 = 3-morpholin-4-yl-propyl, R_3= 2-(3,4-dichloro-phenyl)-ethyl)

1H-NMR; c.s.(ppm): 2.01(b); 2.89-3.18(m); 3.24-3.72(m); 3.97(m); 6.86-7.13(m); 7.22(dd); 7.29-7.38(m); 7.43(dd); 7.52-7.65(m); 8.74(q); 8.78(d); 8.82-8.85(m); 9.67(b); 10.82(b); 10.85(b); 10.89(b).

MS; m/z = 736 (MH^+).

Example 15 - pyrazin-2,3-dicarboxylic acid 2-[[2-(3,4-dichloro-phenyl)-ethyl]-(3-morpholin-4-yl-propyl)-amide] 3-[[2-(1H-indol-3-yl)-ethyl]-amide]

(R_2 = H, and the other substituents are as described in the Example 14)

1H-NMR; c.s.(ppm): 1.55(m); 1.78(m); 2.00(m); 2.29-2.44(m); 2.74-2.82(m); 2.90-3.04(m); 3.22-3.44(m); 3.52-3.70(m); 6.90-7.71(m); 8.74-8.87(m); 8.99-9.07(m); 10.80(s).

MS; m/z = 609 (MH^+).

With a similar procedure the following compounds deriving from asymmetric anhydrides were obtained:

Example 16 - N^1,N^2-*bis*-[2-(1H-indol-3-yl)-ethyl]-N^1,N^2-*bis*-(3-morpholin-4-yl-propyl)-4-nitro-phthalamide

(A = 4-nitro-benzene, X = Y= CO, R_1= R_3= 2-(1H-indol-3-yl)-ethyl, R_2= R_4 = 3-morpholin-4-yl-propyl))

1H-NMR; c.s.(ppm): 1.52-1.78(b); 2.09(m); 2.24-2.36(m); 2.93-3.71(m); 6.68-7.12(m); 7.18-7.36(m); 7.57-7.71(m); 7.86(m); 8.00(m); 8.13-8.34(m); 10.74-10.84(m).

MS; m/z = 750 (MH^+).

Example 17 - naphthalene-1,2-dicarboxylic acid *bis*-[[2-(3,4-dichloro-phenyl)-ethyl]-(3-morpholin-4-yl-propyl)-amide]

(A = naphthalene 1,2 di-substituted, X = Y= CO, R_1= R_3= 2-(3,4-dichloro-phenyl)-ethyl, R_2= R_4 = 3-morpholin-4-yl-propyl))

1H-NMR; c.s.(ppm): 1.37(m); 1.51(m); 1.63-2.02(m); 2.33(m); 2.71-3.41(m); 3.51(m); 3.59(m); 3.68(m); 3.84(m); 6.68(m); 6.91-6.97(m); 7.17(ml; 7.23(m); 7.31-7.46(m); 7.53(m); 7.60(m); 7.67(s); 7.95-8.05(m).

MS; m/z = 813 (MH^+).

Example 18 - N^1,N^2-*bis*-[2-(1H-indol-3-yl)-ethyl N^1,N^2-*bis*-(2-morpholin-4-yl-ethyl)-4-nitro-phthalamide

(R_2= R_4 = 2-morpholin-4-yl-ethyl, and the other substituents are as defined in Example 16)

1H-NMR; c.s.(ppm): 2.15(m); 2.35-2.4(m); 2.54(m); 2.74-3.24(m); 3.33-3.76(m); 6.68-7.41(m); 7.52-7.89(m); 8.15-8.34(m); 10.74-10.83(m).

MS; m/z = 722 (MH^+).

Example 19 - N^1,N^2-*bis*-[2-(1H-indol-3-yl)-ethyl]-N^1,N^2-*bis*-(3-morpholin-4-yl-propyl)-3-nitro-phthalamide

(A = 3-nitro-benzene, and the other substituents are as defined in Example 16)

1H-NMR; c.s.(ppm): c.s.(ppm): 1.79-2.10(m); 2.75-4.03(m); 6.77-6.85(m); 6.92(m); 6.98-7.11(m); 7.18-7.38(m); 7.47(d); 7.55-7.69(m); 7.81-7.92(m); 8.29-8.39(m); 9.86(b); 10.78(b); 10.81(b); 10.83(b); 10.85(b); 10.90(b).

MS; m/z = 750.5 (MH^+).

Example 20 - N^1,N^2-*bis*-[2-(3,4-dichloro-phenyl)-ethyl]-4-hydroxy-N^1,N^2-*bis*-(3-morpholin-4-yl-propyl)-phthalamide

(A = 4-hydroxy-benzene, X = Y= CO, R_1= R_3= 2-(3,4-dichloro-phenyl)-ethyl, R_2= R_4 = 3-morpholin-4-yl-propyl))

1H-NMR; c.s.(ppm): 1.59-1.70(b); 2.10(b); 2.28(b); 2.33(b); 2.83(b); 3.10(b); 3.48-3.57(m); 6.58(b); 6.78(m); 6.97-7.10(m); 7.25-7.35(m); 7.48-7.57(m); 9.92(s).

MS; m/z = 779 (MH^+).

Example 21 - 4-Hydroxy-N^1,N^2-*bis*-[2-(1H-indol-3-yl)-ethyl]-N^1,N^2-*bis*-(3-morpholin-4-yl-propyl)-phthalamide

(A = 4-hydroxy-benzene, and the other substituents are as defined in Example 16)

1H-NMR; c.s.(ppm): 1.68(m,4H); 2.10(b); 2.24-2.37(m,6H); 2.92(m,4H); 3.17(m,2H); 3.38(b); 3.56(b,4H); 6.66(d); 6.75-6.86(m); 6.89(t); 6.94-7.19(m); 7.27-7.34(m,2H); 7.57(d); 7.62(t); 9.89(b); 9.94(b); 9.95(b); 10.74-10.81(m).

MS; m/z = 721 (MH^+).

Example 22 - N^1,N^2-*bis*-[2-(3,4-dichloro-phenyl)-ethyl]-N^1,N^2-*bis*-(3-morpholin-4-yl-propyl)-4-nitro-phthalamide

(A = 4-nitro-benzene, and the other substituents are as defined in Example 20)

1H-NMR; c.s.(ppm): 1.98(b); 2.13(b); 2.74-2.94(m); 3.11-3.23(m); 3.33-3.61(m); 3.96(b); 6.81-6.86(m); 7.00(d); 7.06(m); 7.11(m); 7.21(d); 7.29-7.37(m); 7.40-7.45(m); 7.85(dd); 7.99(d); 8.17-8.27(m).

MS; m/z = 808 (MH^+).

Example 23 - pyridin-3,4-dicarboxylic acid *bis*-[[2-(3,4-dichloro-phenyl)-ethyl]-(3-morpholin-4-yl-propyl)-amide]

(A = pyridin 3,4 di-substituted, and the other substituents are as defined in Example 20)

1H-NMR; c.s.(ppm): 1.61-1.75(m,2H); 2.09(m); 2.26-2.35(m); 2.79-2.89(m); 3.02(m); 3.10(m); 3.49(m); 3.56-3.63(m); 7.02(m); 7.21(d); 7.28-7.39(m); 7.49-7.59(m); 8.42(b); 8.52(s); 8.55(s); 8.63(d); 8.67(m).

MS; m/z = 764 (MH^+).

Example 24 - 4-amino-N^1,N^2-*bis*-[2-(1H-indol-3-yl)-ethyl]-N^1,N^2-*bis*-(3-morpholin-4-yl-propyl)-phthalamide

(A = 4-amine-benzene, and the other substituents are as defined in Example 16)

1H-NMR; c.s.(ppm): 1.97(b); 2.96-3.75(b); 3.96(b); 5.68(b); 6.45-6.66(m); 6.83-7.37(m); 7.62(b); 9.65(b); 10.79(b).

MS; m/z = 720.5 (MH^+).

Example 25 - N^1,N^2-*bis*-[2-(1H-indol-3-yl)-ethyl]-4-methanesulphonylamino-N^1,N^2-*bis*-(3-morpholin-4-yl-propyl)-phthalamide

(A = 4-methanesulphonylamino-benzene, and the other substituents are as defined in Example 16)

1H-NMR; c.s.(ppm): 1.88(b); 2.00(b); 2.95(s); 3.00(s); 3.10(s); 3.14(s); 3.22-3.73(m); 3.92-4.01(m); 6.81-7.11(m); 7.18-7.40(m); 7.45(d); 7.61(m); 9.71(b); 10.15-10.28(m); 10.78-10.87(m).

MS; m/z = 798 (MH^+).

Example 26 - toluene-4-sulphonic acid 3,4-*bis*-[[2-(1H-indol-3-yl)-ethyl]-(3-morpholin-4-yl-propyl)-carbamoyl]-phenyl ester

(A = 4-tosylamine-benzene, and the other substituents are as defined in Example 16)

1H-NMR; c.s.(ppm): 1.53-1.75(m); 2.02-2.15(m); 2.18(s); 2.24(b); 2.25(s); 2.30(s); 2.34(s); 2.39(s); 2.82-2.98(m); 3.09(t); 3.16(t); 3.35-3.40(m); 3.54-3.63(m); 6.79-7.48(m); 7.55(d); 7.60(t); 7.73(d); 7.80(d); 10.80(b).

MS; m/z = 875 (MH^+).

Procedure B (from the chlorides of the acids)

82 mg of benzene disulphonyl chloride (0.30 mmol) were added to a mixture containing 0.33 mmol of amine B and 0.33 mmol of amine B1 and 9 ml of dichloromethane, after addition of 3 ml of triethylamine. After stirring for a time ranging between 10 minutes and two hours at room temperature, the solvent and the excess of triethylamine were evaporated, and the crude product was divided

between dichloromethane and a 10% aqueous solution of Na_2CO_3. The organic phase was washed once again with aqueous sodium carbonate, dried on anhydrous sodium sulphate, and filtered; the solvent was evaporated, and the product was purified by column chromatography and/or preparative HPLC.

In this way the following compounds were obtained:

Example 27 - benzene-1,2-disulphonic acid *bis*-[[2-(1H-indol-3-yl)-ethyl]-(3-morpholin-4-yl-propyl)-amide]

(A = benzene, X = Y= SO_2 , R_1= R_3= 2-(1H-indol-3-yl)-ethyl, R_2= R_4 = 3-morpholin-4-yl-propyl)

1H-NMR; c.s.(ppm): 1.65(qt,4H); 2.15-2.20(m,12H); 2.95(m,4H); 3.39(t,4H); 3.47(t,8H); 3.56(m, 4H); 6.93(td,2H); 7.05(td,2H); 7.15(d,2H); 7.32(d,2H); 7.44(d,2H); 7.78(m,2H); 8.01(m,2H); 10.83(d,2H).

MS; m/z = 777.5 (MH^+).

Example 28 - benzene-1,2-disulphonic acid *bis*-[[2-(1H-indol-3-yl)-ethyl]-(2-morpholin-4-yl-ethyl)-amide]

(A = benzene, X = Y= SO_2 , R_1= R_3= 2-(1H-indol-3-yl)-ethyl, R_2= R_4 = 2-morpholin-4-yl-ethyl)

1H-NMR; c.s. (ppm): 2.31 (b, 4H); 2.44 (t, 2H); 2.98 (t, 2H); 3.47 (t, 4H); 3.52 (t, 2H); 3.57 (m, 2H); 6.93 (t, 1H); 7.04 (t, 1H); 7.14 (d, 1H); 7,32 (d, 1H); 7.45 (d, 1H); 7.76 (m, 1H); 8.08 (m, 1H); 10.82 (b, 1H).

MS; m/z = 749 (MH^+).

With a similar procedure the following compounds were obtained:

Example 29 - *N,N'-bis*-[2-(1H-indol-3-yl)-ethyl *N,N'-bis*-(3-morpholin-4-yl-propyl)-phthalamide

(A = benzene, and the other substituents are as defined in Example 16)

1H-NMR; c.s.(ppm): 1.61-1.79(m,2H); 2.03-2.11(m,3H); 2.23-2.35(m,3H); 2.89-3.02(m,2H); 3.16(dt,1H); 3.33-3.39(m); 3.46(m,1H); 3.55-3.66(m,2H); 6.80(q); 6.89(t); 6.94-7.08(m); 7.18-7.39(m); 7.45(m); 7.58(d); 7.63(d).

MS; m/z = 705 (MH^+).

Example 30 - *N,N'-bis*-[2-(3,4-dichloro-phenyl)-ethyl *N,N'-bis*-(3-morpholin-4-yl-propyl)-phthalamide

(A = benzene, X = Y= CO, R_1= R_3= 2-(3,4-dichloro-phenyl)-ethyl, R_2= R_4 = 3-

morpholin-4-yl-propyl)

1H-NMR; c.s.(ppm): 1.62(b,1H); 1.70(t,1H); 2.07(m,3H); 2.25-2.34(m,3H); 2.77-2.88(m,2H); 3.09(q,1H); 3.32(b); 3.49(t,1H); 3.57(m,2H); 6.98(td); 7.16(d); 7.25(dd); 7.29(m); 7.40-7.45(m); 7.49(dd); 7.53-7.59(m).

MS; m/z = 763 (MH^+).

Example 31 - *N*-[2-(1H-*indol*-3-yl)-ethyl]-*N*-methyl-*N'*-(2-morpholin-4-yl-ethyl)-*N'*-(2-naphthalene-2-yl-ethyl)-phthalamide

(A = benzene, X = Y= CO, R_1= 2-(1H-*indol*-3-yl)-ethyl , R_2= methyl, R_3= 2-naphthalene-2-yl-ethyl, R_4 = 3-morpholin-4-yl-propyl)

1H-NMR; c.s.(ppm): 2.11(b,1H); 2.16(b,1H); 2.33-2.53(m,4H); 2.77(s); 2.82(s); 2.88-3.07(m); 3.00(s); 3.02(s); 3.16(t); 3.21(t); 3.37(t); 3.42-3.47(m); 3.52-3.58(m); 3.62-3.73(m,2H); 6.78(m); 6.90(t); 6.94-7.08(m); 7.12(t); 7.21(s); 7.29(t); 7.32-7.54(m); 7.62(t); 7.73-7.89(m); 10.76(b); 10.77(b); 10.81(b); 10.82(b).

MS; m/z = 589 (MH^+).

Example 32 - *N,N'-bis*-[2-(3,4-dichloro-phenyl)-ethyl]-*N,N'-bis*-(2-morpholin-4-yl-ethyl)-phthalamide

(R_2= R_4 = 2-morpholin-4-yl-ethyl, and the other substituents are as defined in Example 30)

1H-NMR; c.s.(ppm): 2.16(b,2H); 2.35-2.47(m,4H); 2.80-2.89(m,2H); 3.16(m,1H); 3.45-3.62(m); 6.97(t); 7.14(m); 7.27-7.35(m); 7.39-7.50(m); 7.55-7.60(m).

MS; m/z = 735 (MH^+).

Example 33 - *N,N'-bis*-[2-(1H-indol-3-yl)-ethyl]-*N*-methyl-*N'*-(3-thiomorpholin-4-yl-propyl)-phthalamide

(A = benzene, X = Y= CO, R_1= R_3= 2-(1H-*indol*-3-yl)-ethyl , R_2= methyl, R_4 =3-thiomorpholin-4-yl-propyl)

1H-NMR; c.s.(ppm): 1.55-1.75(m); 2.33(s); 2.36(s); 2.42(m); 2.52-2.64(m); 2.77(s); 2.83(s); 2.98(s); 3.01(s); 3.10(m); 3.16(m); 3.27-3.35(m); 3.45(b); 3.60-3.69(m); 6.77-6.82(m); 6.91(m); 6.95-7.08(m); 7.15-7.23(m); 7.26-7.38(m); 7.41-7.50(m); 7.56-7.64(m); 10.74-10.82(m).

MS; m/z = 608 (MH^+).

Example 34 - *N,N'-bis*-[2-(1H-indol-3-yl)-ethyl]-*N,N'-bis*-(3-thiomorpholin-4-yl-propyl)-phthalamide

(A = benzene, X = Y= CO, R_1= R_3= 2-(1H-*ind*ol-3-yl)-ethyl , R_2= R_4 =3-thiomorpholin-4-yl-propyl)

1H-NMR; c.s.(ppm): 1.85(b); 2.02(b); 2.77-3.77(m); 6.77-7.11(m); 7.19(d); 7.22(m); 7.28-7.52(m); 7.60(d); 7.64(d); 9.49(b); 10.78(b); 10.81(b); 10.84(b); 10.87(b).

MS; m/z = 737.5 (MH^+).

Example 35 - *N*-(2-[1,4']bipiperidinyl-1'-yl-ethyl)-*N,N'-bis*-[2-(1H-indol-3-yl)-ethyl]-*N*-methyl-phthalamide

(A = benzene, X = Y= CO, R_1= R_3= 2-(1H-*ind*ol-3-yl)-ethyl , R_2= methyl, R_4 =2-[1,4']Bipiperidinyl-1'-yl-ethyl)

1H-NMR; c.s.(ppm): 1.40(b); 1.68(b); 1.84(b); 2.12(b); 2.23(b); 2.31(b); 2.84(s); 2.87(s); 3.03(s); 3.06(s); 2.77-3.14(b); 3.27-3.87(b); 6.76-6.83(m); 6.91-7.17(m); 7.20-7.23(m); 7.29-7.66(m); 9.45(b); 10.78-10.88(m).

MS; m/z = 659 (MH^+).

Example 36 - *N,N'-bis*-(3-[1,4']bipiperidinyl-1'-yl-propyl)-*N,N'-bis*-[2-(1H-indol-3-yl)-ethyl]-phthalamide

(A = benzene, X = Y= CO, R_1= R_3= 2-(1H-*ind*ol-3-yl)-ethyl , R_2= R_4 =3-[1,4']Bipiperidinyl-1'-yl-propyl)

1H-NMR; c.s.(ppm): 1.41(b); 1.62-2.05(m); 2.24(m); 2.73-3.70(m); 6.76-7.13(m); 7.18(d); 7.22(d); 7.30(dd); 7.34-7.52(m); 7.60(d); 7.66(d); 9.58-9.80(b); 10.78(bd); 10.82(d); 10.85(d); 10.92(d).

MS; m/z = 868. (MH^+).

Example 37 - *N,N'-bis*-(2-morpholin-4-yl-ethyl *N,N'-bis*-(2-naphthalene-2-yl-ethyl)-phthalamide

(A = benzene, X = Y= CO, R_1= R_3= 2-naphthalene-2-yl-ethyl, R_2= R_4 =2-morpholin-4-yl-ethyl)

1H-NMR; c.s.(ppm): 2.15(m,2H); 2.37-2.45(m); 2.53(q); 2.97-3.09(m,2H); 3.19(dt;1H); 3.37-3.47(m,3H); 3.55(m); 3.71(m,1H); 7.07-7.16(m,1H); 7.37(m,1H); 7.42-7.53(m); 7.73-7.89(m).

MS; m/z = 699 (MH^+).

Example 38 - *N,N'-bis*-[2-(1H-indol-3-yl)-ethyl *N,N'-bis*-(2-morpholin-4-yl-ethyl)-phthalamide

(A = benzene, X = Y= CO, R_1= R_3= 2-(1H-*ind*ol-3-yl)-ethyl , R_2= R_4 =2-morpholin-4-yl-ethyl)

1H-NMR; c.s.(ppm): 2.09-2.16(m); 2.34-2.44(m); 2.53(t); 2.91-3.02(m); 3.14-3.23(m); 3.33-3.58(m); 3.64(b); 3.69(b); 6.80(q); 6.90(t); 6.95-7.08(m); 7.22(m); 7.27-7.40(m); 7.46(m); 7.59(d); 7.64(d); 10.74(b); 10.76(b); 10.79(b); 10.81(b).

MS; m/z = 677 (MH^+).

Example 39 - *N*-[2-(1H-*ind*ol-3-yl)-ethyl]-*N,N'-bis*-(2-morpholin-4-yl-ethyl)-*N'*-(2-naphthalene-2-yl-ethyl)-phthalamide

(A = benzene, X = Y= CO, R_1= 2-(1H-*ind*ol-3-yl)-ethyl , R_3= 2-naphthalene-2-yl-ethyl, R_2= R_4 =2-morpholin-4-yl-ethyl)

1H-NMR; c.s.(ppm): 2.14(t); 2.35-2.43(m); 2.54(m); 2.91-3.09(m); 3.14-3.23(m); 3.32-3.74(m); 6.76-7.54(m); 7.61(d); 7.64(d); 7.74-7.89(m); 10.74(b); 10.76(b); 10.80(b); 10.82(b).

MS; m/z = 688 (MH^+).

Example 40 - *N,N'-bis*-[2-(5-fluoro-1H-indol-3-yl)-ethyl]-*N,N'-bis*-(3-morpholin-4-yl-propyl)-phthalamide

(A = benzene, X = Y= CO, R_1= R_3= 2-(5-Fluoro-1H-*ind*ol-3-yl)-ethyl , R_2= R_4 =3-morpholin-4-yl-propyl)

1H-NMR; c.s.(ppm): 1.88(b); 2.03(b); 2.96(b); 3.06-3.38(m); 3.43-3.80(m); 3.90-4.02(m); 6.64(dd); 6.72(d); 6.82-6.95(m); 7.09(d); 7.11(d); 7.25-7.51(m); 9.77(b); 10.90(d); 10.92(d); 10.95(d); 10.99(d).

MS; m/z = 741 (MH^+).

Example 41 - *N,N'-bis*-[2-(1H-indol-3-yl)-ethyl]-*N*-methyl-*N'*-(3-morpholin-4-yl-propyl)-phthalamide

(A = benzene, X = Y= CO, R_1= R_3= 2-(1H-*ind*ol-3-yl)-ethyl , R_2= methyl, R_4 =3-morpholin-4-yl-propyl)

1H-NMR; c.s.(ppm): 1.58-1.78(m); 2.01-2.09(m); 2.25-2.35(m); 2.78(s); 2.83(s); 2.84-3.02(m); 2.98(s); 3.01(s); 3.13(t); 3.19(t); 3.27-3.41(m); 3.47(b); 3.57(m); 3.60-3.69(m); 6.79(m); 6.91(m); 6.95-7.09(m); 7.16(d); 7.20(d); 7.26-7.46(m); 7.61(m); 1074-10.82(m).

MS; m/z = 592 (MH^+).

Example 42 - *N,N'-bis*-[2-[*bis*-(2-methoxy-ethyl)-amino]-ethyl]- *N,N'-bis*-[2-(1H-

indol-3-yl)-ethyl]-phthalamide

(A = benzene, X = Y= CO, R_1= R_3= 2-(1H-*ind*ol-3-yl)-ethyl , R_2= R_4 =2-[*bis*-(2-methoxy-ethyl)-amino]-ethyl)

1H-NMR; c.s.(ppm): 2.36-2.44(m); 2.56-2.74(m); 2.96(b); 3.10(s); 3.12(s); 3.09-3.18(m); 3.15(s); 3.22(s); 3.35(t); 3.40(t); 3.48(m); 3.62(b); 6.79(m); 6.88-7.08(m); 7.19-7.39(m); 7.44-7.51(m); 7.58(d); 7.64(d); 10.74(d); 10.76(d); 10.80(d); 10.81(d).

MS; m/z = 769 (MH^+).

Example 43 - *N*-(2-{4-[*N*-(2-*tert*-butyl-phenyl)-carbamimidoyl]-piperazin-1-yl}-ethyl)-*N*,*N*'-*bis*-[2-(1H-indol-3-yl)-ethyl]-*N*'-methyl-phthalamide

(A = benzene, X = Y= CO, R_1= R_3= 2-(1H-*ind*ol-3-yl)-ethyl , R_2= methyl, R_4 =2-{4-[*N*-(2-*tert*-butyl-phenyl)-carbamidoyl]-piperazin-1-yl}-ethyl)

MS; m/z = 751(MH^+).

Example 44 - *N*-(2-{4-[*N*-(2-*tert*-butyl-phenyl)-*N*'-methyl-carbamimidoyl]-piperazin-1-yl}-ethyl)-*N*,*N*'-*bis*-[2-(1H-indol-3-yl)-ethyl]-*N*'-methyl-phthalamide

(R_4 =2-{4-[*N*-(2-*tert*-butyl-phenyl)- *N*'-methyl -carbamidoyl]-piperazin-1-yl}-ethyl), and the other substituents as in Example 43)

MS; m/z = 765 (MH^+).

Example 45 - *N*-(2-{4-[*N*-(2-*tert*-butyl-phenyl)-*N*'-methyl-carbamimidoyl]-piperazin-1-yl}-ethyl)-*N*'-[2-(3,4-dichloro-phenyl)-ethyl]-*N*-[2-(1H-indol-3-yl)-ethyl]-*N*'-methyl-phthalamide

(A = benzene, X = Y= CO, R_1= 2-(3,4-dichloro-phenyl)-ethyl, R_3= 2-(1H-*ind*ol-3-yl)-ethyl , R_2= methyl, R_4 =2-{4-[*N*-(2-*tert*-butyl-phenyl)- *N*'-methyl -carbamidoyl]-piperazin-1-yl}-ethyl)

MS; m/z = 794 (MH^+).

Example 46 - *N*-[2-(3,4-dichloro-phenyl)-ethyl]-*N*'-[2-(1H-indol-3-yl)-ethyl]-*N*-methyl-*N*'-[2-(4-phenylacetyl-piperazin-1-yl)-ethyl]-phthalamide

(R_4 = 2-(4-phenylacetyl-piperazin-1-yl)-ethyl, and the other substituents as in Example 45)

MS; m/z = 724 (MH^+).

Example 47 - *N*,*N*'-*bis*-[2-(1H-indol-3-yl)-ethyl]-*N*-methyl-*N*'-{2-[4-(tricyclo[3.3.1.1^{0,0}]decane-1-carbonyl)-piperazin-1-yl]-ethyl}-phthalamide

(A = benzene, X = Y= CO, R_1= R_3= 2-(1H-*ind*ol-3-yl)-ethyl , R_2= H, R_4 = {2-[4-(tricyclo[3.3.1.1^{0,0}]decane-1-carbonyl)-piperazin-1-yl]-ethyl } said also 2-(4-(adamantan-1-carbonyl)-piperazin-1-yl)-ethyl

MS; m/z = 739 (MH^+).

Example 48 - *N*,*N*'-*bis*-[2-(1H-indol-3-yl)-ethyl]-*N*-methyl-*N*'-{2-[4-(tricyclo[3.3.1.1^{0,0}]dec-1-yl-acetyl)-piperazin-1-yl]-ethyl}-phthalamide

(R_4 = {2-[4-(tricyclo[3.3.1.1^{0,0}]dec-1-yl-acety)-piperazin-1-yl]-ethyl } said also 2-(4-(adamantan-1-yl-acetyl)-piperazin-1-yl)-ethyl, and the other substituents as in Example 47)

MS; m/z = 753 (MH^+).

Example 49 - *N*-[2-(4-acetyl-piperazin-1-yl)-ethyl]-*N*,*N*'-*bis*-[2-(1H-indol-3-yl)-ethyl]-*N*'-methyl-phthalamide

(A = benzene, X = Y= CO, R_1= R_3= 2-(1H-*ind*ol-3-yl)-ethyl , R_2= methyl, R_4 =2-(4-acetyl-piperazin-1-yl)-ethyl)

MS; m/z = 619 (MH^+).

Example 50 - *N*,*N*'-*bis*-[2-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-ethyl]-*N*,*N*'-*bis*-[2-(1H-indol-3-yl)-ethyl]-phthalamide

(A = benzene, X = Y= CO, R_1= R_3= 2-(1H-*ind*ol-3-yl)-ethyl , R_2= R_4 =2-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-ethyl)

MS; m/z = 789 (MH^+).

Example 51 - *N*-[2-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-ethyl]-*N*,*N*'-*bis*-[2-(1H-indol-3-yl)-ethyl]-*N*'-methyl-phthalamide

(R_2= methyl, and the other substituents as in Example 50)

MS; m/z = 634 (MH^+).

Example 52: *N*-[2-[4-(Butane-1-sulfonyl)-piperazin-1-yl]-ethyl]-*N*,*N*'-bis-[2-(1*H*-Indol-3-yl)-ethyl]-*N*'-methyl-phthalamide

(A = benzene, X = Y= CO, R_1= R_3= 2-(1*H*-Indol-3-yl)-ethyl, R_2= methyl, R_4 = 2-[4-(Butane-1-sulfonyl)-piperazin-1-yl]-ethyl

MS; m/z = 697 (MH+)

Example 53: *N*-[2-(4-Allylcarbamoyl-piperazin-1-yl)-ethyl]-*N*,*N*'-bis-[2-(1*H*-Indol-3-yl)-ethyl]-*N*'-methyl-phthalamide

(R_4 = 2-(4-Allylcarbamoyl-piperazin-1-yl)-ethyl and the other substituents are as

defined in Example 52)

MS; m/z = 660 (MH+)

Example 54: *N,N'*-Bis-[2-(1*H*-Indol-3-yl)-ethyl]-*N*-methyl-*N'*-[2-(4-thiomorpholin-4-yl-methyl-piperidin-1-yl)-ethyl]-phthalamide

(R_4 = 2-(4-thiomorpholin-4-ylmethyl-piperidin-1-yl)-ethyl and the other substituents are as defined in Example 52)

1H-NMR; c.s.(ppm) 0.84-1.13(m); 1.31-1.81(m); 1.82-2.15(m); 2.26-2.60(m); 2.74-3.05(m); 3.31-3.39(m); 3.49-3.69(m); 6.71-7.79(m); 10.70-10.90(m).

MS; m/z = 691 (MH+)

Example 55: *N,N'*-Bis-[2-(1*H*-Indol-3-yl)-ethyl]-*N*-methyl-*N'*-[2-[4-(4-nitro-benzenesulfonyl)-piperazin-1-yl]-ethyl]-phthalamide

(R_4 = 2-[4-(4-nitro-benzenesulfonyl)-piperazin-1-yl]-ethyl and the other substituents are as defined in Example 52)

1H-NMR; c.s.(ppm) 2.14-2.27(m); 2.32-2.43(m); 2.68(s); 2.75(s); 2.80(s); 2.77-3.01(m); 2.93(s); 2.99(s); 3.06-3.16(m); 3.22-3.30(m); 3.55-3.68(m); 6.70-7.63(m); 7.90-8.03(m); 8.36-8.45(m); 10.70-10.90(m).

MS; m/z = 762 (MH+)

Example 56 MEN 14054: *N,N'*-Bis-[2-(1*H*-Indol-3-yl)-ethyl]-*N*-methyl-*N'*-[2-(4-phenylmethanesulfonyl-piperazin-1-yl)-ethyl]-phthalamide

(R_4 = 2-(4-phenylmethanesulfonyl-piperazin-1-yl)-ethyl and the other substituents are as defined in Example 52)

1H-NMR; c.s.(ppm) 1.95-2.20(m); 2.30-2.57(m); 2.77(s); 2.82(s); 2.71-3.23(m); 3.33-3.72(m); 4.24-4.46(m); 6.73-7.69(m); 10.70-10.90(m).

MS; m/z = 731 (MH+)

Example 57: *N,N'*-Bis-[2-(1*H*-Indol-3-yl)-ethyl]-*N*-[2-(4-isopropyl-thiocarbamoyl-piperazin-1-yl)-ethyl]-*N'*-methyl-phthalamide

(R_4 = 2-(4-isopropylthiocarbamoyl-piperazin-1-yl)-ethyl and the other substituents are as defined in Example 52)

1H-NMR; c.s.(ppm) 1.08-1.15(m); 2.06-2.18(m); 2.33-2.59(m); 2.77(s); 2.82(s); 2.87-3.04(m); 2.99(s); 3.02(s); 3.16-3.47(m); 3.53-3.77(m); 4.45-4.56(m); 6.72-7.66(m); 10.70-10.90(m).

MS; m/z = 678 (MH+)

Example 58: 3-(4-{2-[[2-(*H*-Indol-3-yl)-ethyl]-(2-[[2-(*H*-indol-3-yl)-ethyl]-methyl-carbamoyl)-benzoyl)-amino]-ethyl)-piperazine-1-sulfonyl)-thiophene-2-carboxylic acid methyl ester

(R_4 = 2-[4-(thiophene-2- (carboxylic acid methyl ester) - 3-sulfonyl)-piperazin-1-yl]-ethyl and the other substituents are as defined in Example 52)

MS; m/z = 781 (MH+)

Example 59: *N,N'*-Bis-[2-(1*H*-Indol-3-yl)-ethyl]-*N*-methyl-*N'*-[2-[4-(thiophene-2-sulfonyl)-piperazin-1-yl]-ethyl]-phthalamide

(R_4 = 2-[4-(thiophene-2-sulfonyl)-piperazin-1-yl]-ethyl and the other substituents are as defined in Example 52)

MS; m/z = 723 (MH+)

Example 60 : *N,N'*-Bis-[2-(1*H*-Indol-3-yl)-ethyl]-*N*-methyl-*N'*-[2-[4-(2-nitro-benzenesulfonyl)-piperazin-1-yl]-ethyl]-phthalamide

(R_4 = 2-[4-(2-nitro-benzenesulfonyl)-piperazin-1-yl]-ethyl and the other substituents are as defined in Example 52)

1H-NMR; c.s.(ppm) 2.15-2.30(m); 2.33-2.57(m); 2.75(s); 2.81(s); 2.84-3.08(m); 2.94(s); 3.01(s); 3.10-3.20(m); 3.47-3.55(m); 3.59-3.69(m); 6.70-8.03(m); 10.70-10.90(m).

MS; m/z = 762 (MH+)

Example 61: *N*-[2-[4-(Benzo[*b*]thiophene-2-carbonyl)-piperazin-1-yl]-ethyl]-*N,N'*-bis-[2-(1*H*-indol-3-yl)-ethyl]-*N'*-methyl-phthalamide

(R_4 = 2-[4-(Benzo[*b*]thiophene-2-carbonyl)-piperazin-1-yl]-ethyl and the other substituents are as defined in Example 52)

1H-NMR; c.s.(ppm) 2.16-2.27(m); 2.38-2.62(m); 2.78(s); 2.83(s); 2.89-3.05(m); 2.99(s); 3.02(s); 3.15-3.44(m); 3.50-3.73(m); 6.73-8.11(m); 10.70-10.90(m).

MS; m/z = 737 (MH+)

Example 62: *N*-[2-[4-(3,5-Dimethyl-isoxazole-4-sulfonyl)-piperazin-1-yl]-ethyl]-*N,N'*-bis-[2-(1*H*-indol-3-yl)-ethyl]-*N'*-methyl-phthalamide

(R_4 = 2-[4-(3,5-Dimethyl-isoxazole-4-sulfonyl)-piperazin-1-yl]-ethyl and the other substituents are as defined in Example 52)

1H-NMR; c.s.(ppm) 2.22(s); 2.25-2.37(m); 2.42(s); 2.53-2.66(m); 2.78(s); 2.82(s); 2.85-3.05(m); 2.98(s); 3.01(s); 3.59-3.70(m); 6.71-7.68(m); 10.70-10.90(m).

MS; m/z = 736 (MH+)

Example 63: *N*-(2-{4-[*N*-(2-*tert*-Butyl-phenyl)-*N*'-furan-2-ylmethyl-carbamimidoyl]-piperazin-1-yl}-ethyl)-*N*,*N*'-bis-[2-(1*H*-indol-3-yl)-ethyl]-*N*'-methyl-phthalamide, acetic acid salt

(R_4 = 2-{4-[*N*-(2-*tert*-Butyl-phenyl)-*N*'-furan-2-ylmethyl-carbamimidoyl]-piperazin-1-yl}-ethyl and the other substituents are as defined in Example 52)

1H-NMR; c.s.(ppm) 1.27-1.34(m);1.90(s); 2.07-2.19(m); 2.31-2.57(m); 2.77(s); 2.82(s); 2.85-3.06(m); 2.99(s); 3.02(s); 3.07-3.44(m); 3.50-3.72(m); 4.06-4.18(m); 5.29-5.49(br); 6.11-6.21(m); 6.30-6.40(m); 6.65-6.78(m); 10.70-10.80(m); 11.80-12.20(br,s).

MS; m/z = 831 (MH+)

Example 64: *N*-(2-{4-[*N*-Furan-2-ylmethyl-*N*'-(2-methylsulfanyl-ethyl)-carbamimidoyl]-piperazin-1-yl}-ethyl)-*N*,*N*'-bis-[2-(1*H*-indol-3-yl)-ethyl]-*N*'-methyl-phthalamide, acetic acid salt

(R_4 = 2-{4-[*N*-Furan-2-ylmethyl-*N*'-(2-methylsulfanyl-ethyl)-carbamimidoyl]-piperazin-1-yl}-ethyl and the other substituents are as defined in Example 52)

1H-NMR; c.s.(ppm) 1.87(s); 1.97(s); 2.00(s), 2.02(s); 2.04(s);2.17-2.26(m); 2.37-2.67(m); 2.77(s); 2.82(s); 2.87-3.05(m); 2.98(s); 3.02(s); 3.12-3.34(m); 3.51-3.72(m); 4.25-4.41(m); 6.24-6.52(m); 6.72-7.81(m); 10.60-10.90(m)

MS; m/z = 773 (MH+)

Example 65: *N*-(2-Benzo[*b*]thiophen-3-yl-ethyl)-*N*'-[2-(4-benzyl-piperazin-1-yl)-ethyl]-*N*'-[2-(1*H*-indol-3-yl)-ethyl]-*N*-methyl-phthalamide

(A = benzene, X = Y= CO, R_1= 2-(1*H*-indol-3-yl)-ethyl, R_2 = 2-(4-benzyl-piperazin-1-yl)-ethyl , R_3= methyl, R_4 = 2-Benzo[*b*]thiophen-3-yl-ethyl

1H-NMR; c.s.(ppm) 2.07-2.58(m); 2.77(s); 2.82(s); 2.86-3.01(m); 2.99(s); 3.02(s); 3.05-3.24(m); 3.27-3.42(m); 3.50-3.56(br); 3.61-3.75(m); 6.72-7.68(m); 7.88-8.03(m); 10.70-10.90(m).

MS; m/z = 684 (MH+)

Example 66: *N*-[2-(4-Benzyl-piperazin-1-yl)-ethyl]-*N*-[2-(1*H*-indol-3-yl)-ethyl]-*N*'-methyl-*N*'-[2-(4-nitro-phenyl)-ethyl]-phthalamide

(R_4 = 2-(4-nitro-phenyl)-ethyl and the other substituents are as defined in Example 65)

1H-NMR; c.s.(ppm) 2.04-2.54(m); 2.73(s); 2.77(s); 2.83-3.06(s); 2.93(s); 2.96(s); 3.11-3.19(m); 3.26-3.47(m); 3.49-3.57(m); 3.60-3.71(m); 6.73-6.81(m); 6.86-7.48(m); 7.54-7.65(m); 8.04-8.21(m); 10.70-10.90(m).

MS; m/z = 673 (MH+)

Example 67 MEN 14421: *N*-[2-(4-Benzyl-piperazin-1-yl)-ethyl]-*N*'-(2-biphenyl-4-yl-ethyl)-*N*-[2-(1*H*-indol-3-yl)-ethyl]-*N*'-methyl-phthalamide

(R_4 = 2-biphenyl-4-yl-ethyl and the other substituents are as defined in Example 65)

1H-NMR; c.s.(ppm) 2.06-2.53(m); 2.76(s); 2.80(s); 2.78-2.98(m); 2.96(s); 2.99(s); 3.11-3.21(m); 3.23-3.46(m); 3.49-3.57(m); 3.58-3.70(m); 6.74-6.81(m); 6.89-7.67(m); 10.80-10.90(m).

MS; m/z = 704 (MH+)

Example	pKi
2	9.1
3	8.6
4	8.0
16	7.7
26	7.8
34	8.4
42	8.0
50	8.1
52	8.2
55	8.3
56	8.5
57	8.5
58	9.0
59	8.6
60	8.7
61	8.3
62	9.2
65	8.7

The compounds that form the subject of the present invention have proven active on tachykinin receptors as antagonists or agonists, and their activity on these receptors has been evaluated by means of *in-vitro* preparations that are by now well known to the person skilled in the art.

In particular, the affinity of the compounds for the human NK2 receptor was evaluated in a binding test using Chinese hamster ovary (CHO) membranes transfected with the NK2 receptor of the human ileum and the radioligand (^{125}I)NKAn at the concentration of 100pM in competition studies, obtaining values of pKi of up to 9.2.

The biological activity on the NK2 receptor was evaluated by means of *in-vitro* functional tests well known to the man skilled in the art, for example those

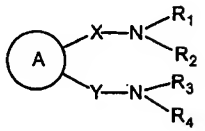
performed on organs isolated from guinea pig (M. Tramontana et al. Eur. J. Pharmacol. 1998, 352, 279-288); P. Santicioli et al. Naunyn Schmieddeberg's Arch. Pharmacol. 1997, 35, 678-688) and/or functional tests on transfected huma cells (P.A. Iredale and J.M. Dickenson, Chapter 17 in "Signal Trasduction Protcols" D.A. Kendall and S.J. Hill eds. ISBN: 0-89603-298-1).

The activity demonstrated by the compounds of the present invention on tachykinin receptors means that they may potentially be used in numerous diseases in which tachykinins play a pathologically important role; these include: asthma, allergic rhinitis, chronic obstructive pulmonary disease, cough, urticaria, inflammation (including that of a neurogenic origin), pain (including neuropathic, visceral and ocular pain), hemicrania, rheumatoid arthritis, pre-menstrual tension, emesis (including emesis resistant to ondansetron), oedema, gastric hypermotility, diseases due to oesophageal reflux, Crohn's disease, problems due to gastric evacuation, ulcerous colitis, the irritable-colon syndrome, hypermotility of the detrusor, urinary incontinence, cystitis, and renal colics.

In particular, the bronchospastic component of asthma, cough, pulmonary irritations, intestinal spasms (for example, in Crohn's disease, in ulcerous colitis or the irritable-colon syndrome), or local spasms of the bladder and of the ureter during cystitis, renal infections and colics can be considered conditions in which the administration of NK2 antagonists may be effective.

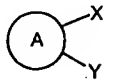
CLAIMS

1. Compounds having the general formula (I)



(I)

in which the group:



is made up of:

a C_{2-12} alkenyl group or an aromatic group in which the two substituents X and Y are bound to two adjacent carbon atoms;

- X and Y, which are the same as or different from one another, represent a -CO- or else -SO_2- group;

- R_1 and R_3, which are the same as or different from one another, represent a -C_{2-5}alkylidene-T-Ar_1 group in which T is a bond or a group chosen from among S, SO or SO_2, and Ar_1 is an aromatic group chosen from among benzene, pyridine, pyrimidine, pyrazine, pyridazine, pyrrole, furan, thiophene, triazole, imidazole, oxazole, thiazole, isoxazole, naphthalene, quinoline, isoquinoline, quinazoline, quinoxaline, cinnoline, phthalazine, indole, isoindole, benzofuran, isobenzofuran, benzothiophene, isobenzothiophene, benzotriazole, benzoimidazole, benzoxazole, benzothiazole, benzoisoxazole, and azulene possibly substituted with one or two groups chosen from among fluoro-, chloro-, bromo-, nitro-, cyano-, hydroxy-, methoxy-, methyl-, trifluoromethyl-, trifluoromethoxy-, amino-, methylamino-, dimethylamino-, acetylamino-, mesylamino-, tosylamino-, tosyloxy-, carboxy-, carboxyamido-, guanidino-, and sulphamido-;

- R_2 and R_4, which are the same as or different from one another, represent a group chosen from among H, -C_{1-5}alkyl, -C_{1-5}alkylidene-NR_5R_6 in which :

R_5 and R_6, which are the same as or different from one another, represent an H, -

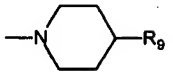
C_{1-5}alkyl, -C_{2-5}alkylidene-Q group in which Q is a group chosen from between OR_7 and NR_7R_8, and in which R_7 and R_8, which are the same as or different from one another, represent an H, -C_{1-5}alkyl group; or NR_7R_8 together represent a group chosen from among piperidine, morpholine, pyrrolidine, thiomorpholine, thiomorpholin-1-oxide, thiomorpholin-1,1-dioxide piperazine, *N*-methyl-piperazine, aziridine,

or else NR_5R_6 together represent a group chosen from among:

a) pyrrolidine, morpholine, thiomorpholine, thiomorpholin-1-oxide, thiomorpholin-1,1-dioxide, guanidine, guanidine mono-substituted or di-substituted with -C_{1-5}alkyl or -C_{1-5}acyl, -NH-CH=NH,

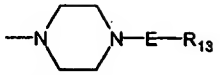
-NH-C(R_{12})=NH groups, where R_{12} is a -C_{1-5} alkyl group;

b) a 4-piperidon ethylene ketal group or else a piperidine of the type



in which R_9 is chosen from among H, -C_{1-5}alkyl, benzyl, OR_{10}, $NR_{10}R_{11}$, and in which R_{10} and R_{11}, which are the same as or different from one another, represent an H, -C_{1-5}alkyl group, or else $NR_{10}R_{11}$ together represent a group chosen from among piperidine, morpholine, pyrrolidine, thiomorpholine, thiomorpholin-1-oxide, thiomorpholin-1,1-dioxide, piperazine, *N*-methyl-piperazine, and aziridine;

c) a piperazine of the type



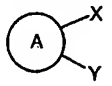
in which E represents a bond or else a group chosen from among -CO-, -SO_2- , -CONH-, -SO_2NH-, and R_{13} is a group chosen from among H, -C_{1-5} alkyl, -$(CH_2)_n$-adamantyl, -$(CH_2)_n$- Ar_2, in which n = 0,1,2 and Ar_2 is an aromatic group chosen from between naphthalene and benzene possibly substituted with 1, 2, 3 groups chosen from among F, Cl, CF_3, OH, OCH_3, $SOCH_3$, OCF_3, CN, C_{1-5}alkyl;

with the limitation that at least one between R_2 and R_4 must always be a -C_{1-5}alkylidene-NR_5R_6 group, as defined above;

the optical isomers, including those deriving from phenomena of atropoisomery, such as pure enantiomers or in racemic or non-racemic mixtures,

the pharmaceutically acceptable salts of these compounds with organic and inorganic acids chosen from the following group: hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, carbonic acid, acetic acid, trifluoroacetic acid, trichloroacetic acid, oxalic acid, malonic acid, malic acid, succinic acid, tartaric acid, citric acid, methanesulphonic acid, *p*-toluenesulphonic acid, maleic acid, and fumaric acid.

2. Compounds according to claim 1 in which the group:



is made up of:

a) an olefin chosen from between:

in which Z and W, which are the same as or different from one another, represent an H, C_{1-5} alkyl group, or else together represent a C_{2-6} alkylidene;

b) an aromatic group Ar, either mono-cyclic or bi-cyclic, in which the substituents X and Y are in an ortho position with respect to one another and are chosen in the group made up of: benzene, pyridine, pyrimidine, pyrazine, pyridazine, pyrrole, furan, thiophene, triazole,

imidazole, oxazole, thiazole, isoxazole, naphthalene, quinoline, isoquinoline, quinazoline, quinoxaline, cinnoline, phthalazine, indole, isoindole, benzofuran, isobenzofuran, benzothiophene, isobenzothiophene, benzotriazole, benzoimidazole, benzoxazole, benzothiazole, and benzoisoxazole,

said aromatic group being possibly further substituted with one, two, three or four groups, which are the same as or different from one another, chosen in the group made up of: fluoro-, chloro-, bromo-, nitro-, cyano-, hydroxy-, methoxy-, methyl-, trifluoromethyl-, trifluoromethoxy-, amino-, methylamino-, dimethylamino-, acetylamino-, mesylamino-, tosylamino-, tosyloxy-, carboxy-, carboxyamido-, guanidino-, and sulphamido-;

and the other substituents are as previously defined.

3. Compounds, according to claim 2, in which:

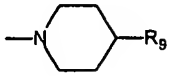
- R_1 and R_3, which are the same as or different from one another, represent a $-C_{2-5}$alkylidene-T-Ar_1 group in which T is a bond or a group chosen from between S and SO, and Ar_1 is an aromatic group chosen from among benzene, naphthalene, quinoline, isoquinoline, quinazoline, quinoxaline, cinnoline, phthalazine, indole, isoindole, benzofuran, isobenzofuran, benzothiophene, isobenzothiophene, benzotriazole, benzoimidazole, benzoxazole, benzothiazole, and benzoisoxazole, possibly substituted with one or two groups chosen from among fluoro-, chloro-, cyano-, hydroxy-, methoxy-, methyl-, trifluoromethyl-, trifluoromethoxy-, amino-, acetylamino-, mesylamino-, tosylamino-, tosyloxy-, guanidino-, and sulphamido-;
- R_2 and R_4, which are the same as or different from one another, represent a group chosen from among H, $-C_{1-5}$alkyl, $-C_{1-5}$alkylidene-NR_5R_6 in which :

R_5 and R_6, which are the same as or different from one another, represent an H, $-C_{1-5}$alkyl, $-C_{2-5}$alkylidene-Q group in which Q is a group chosen from between OR_7 and NR_7R_8 and in which R_7 and R_8, which are the same as or different from one another, represent an H, $-C_{1-5}$alkyl group; or NR_7R_8 together represent a group chosen from among piperidine, morpholine, pyrrolidine, thiomorpholine, thiomorpholin-1-oxide, thiomorpholin-1,1-dioxide, piperazine, *N*-methyl-piperazine, or else NR_5R_6 together represent a group chosen from among:

a) pyrrolidine, morpholine, thiomorpholine, thiomorpholin-1-oxide, thiomorpholin-1,1-dioxide, guanidine, guanidine mono-substituted or di-substituted with $-C_{1-5}$alkyl or $-C_{1-5}$acyl, -NH-CH=NH,

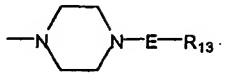
-NH-C(R_{12})=NH groups, where R_{12} is a $-C_{1-5}$ alkyl group;

b) a 4-piperidon ethylene ketal group or else a piperidine of the type



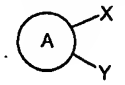
in which R_9 is chosen from among H, $-C_{1-5}$alkyl, benzyl, OR_{10}, $NR_{10}R_{11}$, and in which R_{10} and R_{11}, which are the same as or different from one another, represent an H, $-C_{1-5}$alkyl group, or else $NR_{10}R_{11}$ together represent a group chosen from among piperidine, morpholine, pyrrolidine, thiomorpholine, thiomorpholin-1-oxide, thiomorpholin-1,1-dioxide, piperazine, *N*-methyl-piperazine, and aziridine;

c) a piperazine of the type



in which E represents a bond or else a group chosen from among -CO-, -SO_2-, -CONH-, -SO_2NH-, and R_{13} is a group chosen from among H, - C_{1-5} alkyl, -$(CH_2)_n$- adamantyl, -$(CH_2)_n$- Ar_2, in which n = 0,1,2 and Ar_2 is an aromatic group chosen from between naphthalene and benzene possibly substituted with 1, 2, 3 groups chosen from among F, Cl, CF_3, OH, OCH_3, $SOCH_3$, OCF_3, CN, C_{1-5}alkyl;
with the limitation that at least one between R_2 and R_4 must always be a -C_{1-5}alkylidene-NR_5R_6 group, as defined above, and the other substituents are as defined above.

4. Compounds according to claim 3, of the general formula (I) in which the group:



may be an olefin chosen from between

in which Z and W, which are the same as or different from one another, represent an H, C_{1-5} alkyl group, or else together represent a C_{2-6}alkylidene.

5. Compounds according to claim 4, in which the -C_{2-6} alkylidene part of Z and W is chosen from among -$(CH_2)_3$-, -$(CH_2)_4$-, -$(CH_2)_5$-, -$(CH_2)_6$-; the -C_{2-5}alkylidene part of R_1 and R_3 part is chosen in the -$(CH_2)_2$-, -$(CH_2)_3$-, -$(CH_2)_4$-, isopropylidene, isobutylidene group; the -C_{1-5}alkylidene part in R_2 and R_4 is chosen from among -CH_2-, -$(CH_2)_2$-, -$(CH_2)_3$-, -$(CH_2)_4$-, isopropylidene; -C_{1-5}alkyl is chosen from among methyl, ethyl, propyl, isopropyl, butyl, *ter*-butyl; and -C_{1-5}acyl is chosen from among formyl, acetyl, propanoyl, isopropanoyl.

6. Compounds according to claim 5, in which Z and W, which are the same as or different from one another, are H or methyl or together represent a butylidene group, and X and Y represent a -CO- group.

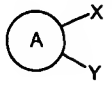
7. The following compounds according to claim 6:

-*cis*-but-2-enedioic acid *bis*-[[2-(3,4-dichloro-phenyl)-ethyl]-(3-morpholin-4-yl-

propyl)-amide];

- cyclohex-1-ene-1,2-dicarboxylic acid *bis*-[[2-(1H-indol-3-yl)-ethyl]-(2-morpholin-4-yl-ethyl)-amide].

8. Compounds according to claim 3, in which the group:



is an aromatic group Ar, either mono-cyclic or bi-cyclic, with the substituents X and Y in an ortho position with respect to one another,
chosen from among benzene, pyridine, pyrimidine, pyrazine, pyridazine, pyrrole, furan, thiophene, triazole, imidazole, oxazole, thiazole, isoxazole, naphthalene, quinoline, isoquinoline, quinazoline, quinoxaline, cinnoline, phthalazine, indole, isoindole, benzofuran, isobenzofuran, benzothiophene, isobenzothiophene, benzotriazole, benzoimidazole, benzoxazole, benzothiazole, and benzoisoxazole, possibly further substituted with one, two, three or four groups, which are the same as or different from one another, chosen from among fluoro-, chloro-, bromo-, nitro-, cyano-, hydroxy-, methoxy-, methyl-, trifluoromethyl-, trifluoromethoxy-, amino-, methylamino-, dimethylamino-, acetylamino-, mesylamino-, tosylamino-, tosyloxy-, carboxy-, carboxyamido-, guanidino-, and sulphamido-.

9. Compounds according to claim 8, in which :

- the aromatic group Ar is chosen in the group made up of: benzene, pyridine, pyrazine, pyrimidine, naphthalene, quinoline, quinazoline, quinoxaline, cinnoline, phthalazine, indole, benzofuran, benzothiophene, benzothiazole, and benzoisoxazole, and is possibly further substituted with one, two, three or four groups, which are the same as or different from one another chosen from among: fluoro-, chloro-, nitro-, hydroxy-, methoxy-, methyl-, trifluoromethyl-, trifluoromethoxy-, amino-, mesylamino-, and guanidino.

10. Compounds according to claim 9 in which :

- the aromatic group Ar is chosen in the group made up of benzene, naphthalene, pyrazine, and pyridine, possibly further substituted with one, two, three or four groups, which are the same as or different from one another, chosen from among : fluoro-, chloro-, nitro-, amino-, hydroxy-, mesylamino-, and tosyloxy.

11. Compounds according to claim 9 in which:

R_1 and R_3, which are the same as or different from one another, represent a $-C_{2-5}$alkylidene-T-Ar_1 group in which T is a bond or a group chosen from between S and SO, and Ar_1 is an aromatic group chosen from among benzene, naphthalene, quinoline, indole, benzofuran, benzothiophene, benzoxazole, and benzothiazole, possibly substituted with one or two groups chosen from among fluoro-, chloro-, cyano-, hydroxy-, methoxy-, methyl-, trifluoromethyl-, trifluoromethoxy-, amino-, acetylamino-, mesylamino-, and guanidino.

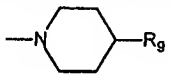
12. Compounds according to claim 9 in which:

R_2 and R_4, which are the same as or different from one another, represent a group chosen from among H, $-C_{1-5}$alkyl, $-C_{1-5}$alkylidene-NR_5R_6, in which :

R_5 and R_6, which are the same as or different from one another, represent an H, $-C_{1-5}$alkyl, $-C_{2-5}$alkylidene-Q group in which Q is an OR_7 group and in which R_7 represents an H, $-C_{1-5}$alkyl group, or else NR_5R_6 together represent a group chosen from among:

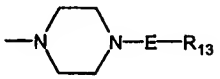
a) pyrrolidine, morpholine, thiomorpholine, thiomorpholin-1-oxide, thiomorpholin-1,1-dioxide, guanidine, guanidine mono-substituted or di-substituted with $-C_{1-5}$alkyl or $-C_{1-5}$acyl, -NH-CH=NH, -NH-C(R_{12})=NH groups , where R_{12} is a $-C_{1-5}$ alkyl group;

b) a 4-piperidone ethylene ketal group or else a piperidine of the type



in which R_9 is chosen from among H, OH, piperidine, morpholine, thiomorpholine, thiomorpholin-1-oxide, thiomorpholin-1,1-dioxide;

c) a piperazine of the type



in which E represents a bond or else a group chosen from between -CO- and -CONH-, and R_{13} is a group chosen from among H, - C_{1-5} alkyl, $-(CH_2)_n$-adamantyl, $-(CH_2)_n$- Ar_2, in which n = 0,1,2 and Ar_2 is a benzene possibly substituted with 1, 2, 3 groups chosen from among F, Cl, CF_3, OH, OCH_3, $SOCH_3$, OCF_3, CN, and C_{1-5}alkyl.

13. Compounds according to claims 9 to 12 in which:

the $-C_{2-5}$alkylidene part of R_1 and R_3 is chosen in the $-(CH_2)_2$-, $-(CH_2)_3$-, $-(CH_2)_4$-, isopropylidene, and isobutylidene group; the $-C_{1-5}$alkylidene part in R_2 and R_4 is chosen from among $-CH_2$-, $-(CH_2)_2$-, $-(CH_2)_3$-, $-(CH_2)_4$-,and isopropylidene;

$-C_{1-5}$alkyl is chosen from among methyl, ethyl, propyl, isopropyl, butyl, *ter*-butyl; and $-C_{1-5}$acyl is chosen from among formyl, acetyl, propanoyl, and isopropanoyl.

14. The following compounds according to claims 10 to 13:

N,N'-bis-[2-(1H-indol-3-yl)-ethyl]-*N*-methyl-*N'*-(2-[4-(3-nitro-phenylcarbamoyl)-piperazin-1-yl]-ethyl)-phthalamide

N-(2-[4-(2-*tert*-butyl-phenylcarbamoyl)-piperazin-1-yl]-ethyl)-*N,N'-bis*-[2-(1H-indol-3-yl)-ethyl]-*N'*-methyl-phthalamide

N-[2-(4-benzyl-piperazin-1-yl)-ethyl]-*N,N'-bis*-[2-(1H-indol-3-yl)-ethyl]-*N'*-methyl-phthalamide

N-[2-(4-benzylcarbamoyl-piperazin-1-yl)-ethyl]-*N,N'-bis*-[2-(1H-indol-3-yl)-ethyl]-*N'*-methyl-phthalamide

N-[2-(4-benzyl-piperazin-1-yl)-ethyl]-*N*-[2-(1H-indol-3-yl)-ethyl]-*N'*-(2-morpholin-4-yl-ethyl)-*N'*-(2-naphthalene-2-yl-ethyl)-phthalamide

N-[3-(4-benzyl-piperazin-1-yl)-propyl]-*N,N'-bis*-[2-(1H-indol-3-yl)-ethyl]-*N'*-methyl-phthalamide

N,N'-bis-[2-(1H-indol-3-yl)-ethyl]-*N*-methyl-*N'*-2-[4-(4-trifluoromethoxy-phenylcarbamoyl)-piperazin-1-yl]-ethyl)-phthalamide

N,N'-bis-[2-(1H-indol-3-yl)-ethyl]-*N*-methyl-*N'*-[2-(4-phenylcarbamoyl-piperazin-1-yl)-ethyl]-phthalamide

N-(2-[4-(3,4-dichloro-phenylcarbamoyl)-piperazin-1-yl]-ethyl)-*N,N'-bis*-[2-(1H-indol-3-yl)-ethyl]-*N'*-methyl-phthalamide

cis-but-2-enedioic acid *bis*-[[2-(3,4-dichloro-phenyl)-ethyl]-(3-morpholin-4-yl-propyl)-amide]

Naphthalene-2,3-dicarboxylic acid *bis*-[[2-(1H-indol-3-yl)-ethyl]-(2-morpholin-4-yl-ethyl)-amide]

Naphthalene-2,3-dicarboxylic acid *bis*-[[2-(5-fluoro-1H-indol-3-yl)-ethyl]-(3-morpholin-4-yl-propyl)-amide]

Cyclohex-1-ene-1,2-dicarboxylic acid *bis*-[[2-(1H-indol-3-yl)-ethyl]-(2-morpholin-4-

yl-ethyl)-amide]

Pyrazin-2,3-dicarboxylic acid 2-[[2-(3,4-dichloro-phenyl)-ethyl]-(3-morpholin-4-yl-propyl)-amide] 3-[[2-(1H-indol-3-yl)-ethyl]-(3-morpholin-4-yl-propyl)-amide]

Pyrazin-2,3-dicarboxylic acid 2-[[2-(3,4-dichloro-phenyl)-ethyl]-(3-morpholin-4-yl-propyl)-amide] 3-[[2-(1H-indol-3-yl)-ethyl]-amide

N^1,*N*^{2}-*bis*-[2-(1H-indol-3-yl)-ethyl]-*N*^{1},*N*^{2}-*bis*-(3-morpholin-4-yl-propyl)-4-nitro-phthalamide

Naphthalene-1,2-dicarboxylic acid *bis*-[[2-(3,4-dichloro-phenyl)-ethyl]-(3-morpholin-4-yl-propyl)-amide]

N^1,*N*^{2}-*bis*-[2-(1H-indol-3-yl)-ethyl *N*^{1},*N*^{2}-*bis*-(2-morpholin-4-yl-ethyl)-4-nitro-phthalamide

N^1,*N*^{2}-*bis*-[2-(1H-indol-3-yl)-ethyl]-*N*^{1},*N*^{2}-*bis*-(3-morpholin-4-yl-propyl)-3-nitro-phthalamide

N^1,*N*^{2}-*bis*-[2-(3,4-dichloro-phenyl)-ethyl]-4-hydroxy-*N*^{1},*N*^{2}-*bis*-(3-morpholin-4-yl-propyl)-phthalamide

4-Hydroxy-*N*^{1},*N*^{2}-*bis*-[2-(1H-indol-3-yl)-ethyl]-*N*^{1},*N*^{2}-*bis*-(3-morpholin-4-yl-propyl)-phthalamide

N^1,*N*^{2}-*bis*-[2-(3,4-dichloro-phenyl)-ethyl]-*N*^{1},*N*^{2}-*bis*-(3-morpholin-4-yl-propyl)-4-nitro-phthalamide

Pyridin-3,4-dicarboxylic acid *bis*-[[2-(3,4-dichloro-phenyl)-ethyl]-(3-morpholin-4-yl-propyl)-amide]

4-amino-*N*^{1},*N*^{2}-*bis*-[2-(1H-indol-3-yl)-ethyl]-*N*^{1},*N*^{2}-*bis*-(3-morpholin-4-yl-propyl)-phthalamide

N^1,*N*^{2}-*bis*-[2-(1H-indol-3-yl)-ethyl]-4-methanesulfonylamino-*N*^{1},*N*^{2}-*bis*-(3-morpholin-4-yl-propyl)-phthalamide

Toluene-4-sulphonic acid 3,4-*bis*-[[2-(1H-indol-3-yl)-ethyl]-(3-morpholin-4-yl-propyl)-carbamoyl]-phenyl ester

Benzene-1,2-disulphonic acid *bis*-[[2-(1H-indol-3-yl)-ethyl]-(3-morpholin-4-yl-propyl)-amide]

Benzene-1,2-disulphonic acid *bis*-[[2-(1H-indol-3-yl)-ethyl]-(2-morpholin-4-yl-ethyl)-amide]

N,N'-bis-[2-(1H-indol-3-yl)-ethyl *N,N'-bis*-(3-morpholin-4-yl-propyl)-phthalamide

N,N'-bis-[2-(3,4-dichloro-phenyl)-ethyl *N,N'-bis*-(3-morpholin-4-yl-propyl)-phthalamide

N-[2-(1H-*ind*ol-3-yl)-ethyl]-*N*-methyl-*N'*-(2-morpholin-4-yl-ethyl)-*N'*-(2-naphthalene-2-yl-ethyl)-phthalamide

N,N'-bis-[2-(3,4-dichloro-phenyl)-ethyl]-*N,N'-bis*-(2-morpholin-4-yl-ethyl)-phthalamide

N,N'-bis-[2-(1H-indol-3-yl)-ethyl]-*N*-methyl-*N'*-(3-thiomorpholin-4-yl-propyl)-phthalamide

N,N'-bis-[2-(1H-indol-3-yl)-ethyl]-*N,N'-bis*-(3-thiomorpholin-4-yl-propyl)-phthalamide

N-(2-[1,4']Bipiperidinyl-1'-yl-ethyl)-*N,N'-bis*-[2-(1H-indol-3-yl)-ethyl]-*N'*-methyl-phthalamide

N,N'-bis-(3-[1,4']bipiperidinyl-1'-yl-propyl)-*N,N'-bis*-[2-(1H-indol-3-yl)-ethyl]-phthalamide

N,N'-bis-(2-morpholin-4-yl-ethyl *N,N'-bis*-(2-naphthalene-2-yl-ethyl)-phthalamide

N,N'-bis-[2-(1H-indol-3-yl)-ethyl *N,N'-bis*-(2-morpholin-4-yl-ethyl)-phthalamide

N-[2-(1H-*ind*ol-3-yl)-ethyl]-*N,N'-bis*-(2-morpholin-4-yl-ethyl)-*N'*-(2-naphthalene-2-yl-ethyl)-phthalamide

N,N'-bis-[2-(5-fluoro-1H-indol-3-yl)-ethyl]-*N,N'-bis*-(3-morpholin-4-yl-propyl)-phthalamide

N,N'-bis-[2-(1H-indol-3-yl)-ethyl]-*N*-methyl-*N'*-(3-morpholin-4-yl-propyl)-phthalamide

N,N'-bis-[2-[*bis*-(2-methoxy-ethyl)-amino]-ethyl]- *N,N'-bis*-[2-(1H-indol-3-yl)-ethyl]-phthalamide

N-(2-{4-[*N*-(2-*tert*-butyl-phenyl)-carbamimidoyl]-piperazin-1-yl}-ethyl)-*N,N'-bis*-[2-(1H-indol-3-yl)-ethyl]-*N'*-methyl-phthalamide

N-(2-{4-[*N*-(2-*tert*-butyl-phenyl)-*N'*-methyl-carbamimidoyl]-piperazin-1-yl}-ethyl)-*N,N'-bis*-[2-(1H-indol-3-yl)-ethyl]-*N'*-methyl-phthalamide

N-(2-{4-[*N*-(2-*tert*-butyl-phenyl)-*N'*-methyl-carbamimidoyl]-piperazin-1-yl}-ethyl)-*N'*-[2-(3,4-dichloro-phenyl)-ethyl]-*N*-[2-(1H-indol-3-yl)-ethyl]-*N'*-methyl-phthalamide

N-[2-(3,4-dichloro-phenyl)-ethyl]-*N'*-[2-(1H-indol-3-yl)-ethyl]-*N*-methyl-*N'*-[2-(4-phenylacetyl-piperazin-1-yl)-ethyl]-phthalamide

N,N'-bis-[2-(1H-indol-3-yl)-ethyl]-*N*-methyl-*N'*-{2-[4-(tricyclo[3.3.1.1^{0,0}]decane-1-

carbonyl)-piperazin-1-yl]-ethyl}-phthalamide

N,N'-bis-[2-(1H-indol-3-yl)-ethyl]-*N*-methyl-*N'*-{2-[4-(tricyclo[3.3.1.1^{0,0}]dec-1-yl-acetyl)-piperazin-1-yl]-ethyl}-phthalamide

N-[2-(4-acetyl-piperazin-1-yl)-ethyl]-*N,N'-bis*-[2-(1H-indol-3-yl)-ethyl]-*N'*-methyl-phthalamide

N,N'-bis-[2-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-ethyl]-*N,N'-bis*-[2-(1H-indol-3-yl)-ethyl]-phthalamide

N-[2-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-ethyl]-*N,N'-bis*-[2-(1H-indol-3-yl)-ethyl]-*N'*-methyl-phthalamide

N-[2-[4-(Butane-1-sulfonyl)-piperazin-1-yl]-ethyl)-*N,N'*-bis-[2-(1*H*-indol-3-yl)-ethyl]-*N'*-methyl-phthalamide

N-[2-(4-Allylcarbamoyl-piperazin-1-yl)-ethyl]-*N,N'*-bis-[2-(1*H*-indol-3-yl)-ethyl]-*N'*-methyl-phthalamide

N,N'-Bis-[2-(1*H*-indol-3-yl)-ethyl]-*N*-methyl-*N'*-[2-(4-thiomorpholin-4-yl-methyl-piperidin-1-yl)-ethyl]-phthalamide

N,N'-Bis-[2-(1*H*-indol-3-yl)-ethyl]-*N*-methyl-*N'*-{2-[4-(4-nitro-benzenesulfonyl)-piperazin-1-yl]-ethyl)-phthalamide

N,N'-Bis-[2-(1*H*-indol-3-yl)-ethyl]-*N*-methyl-*N'*-[2-(4-phenylmethanesulfonyl-piperazin-1-yl)-ethyl]-phthalamide

N,N'-Bis-[2-(1*H*-indol-3-yl)-ethyl]-*N*-{2-(4-isopropyl-thiocarbamoyl-piperazin-1-yl)-ethyl]-*N'*-methyl-phthalamide

3-(4-{2-[[2-(*H*-Indol-3-yl)-ethyl]-(2-{[2-(*H*-indol-3-yl)-ethyl]-methyl-carbamoyl}-benzoyl)-amino]-ethyl)-piperazine-1-sulfonyl)-thiophene-2-carboxylic acid methyl ester

N,N'-Bis-[2-(1*H*-indol-3-yl)-ethyl]-*N*-methyl-*N'*-{2-[4-(thiophene-2-sulfonyl)-piperazin-1-yl]-ethyl}-phthalamide

N,N'-Bis-[2-(1*H*-indol-3-yl)-ethyl]-*N*-methyl-*N'*-{2-[4-(2-nitro-benzenesulfonyl)-piperazin-1-yl]-ethyl}-phthalamide

N-{2-[4-(Benzo[*b*]thiophene-2-carbonyl)-piperazin-1-yl]-ethyl}-*N,N'*-bis-[2-(1*H*-indol-3-yl)-ethyl]-*N'*-methyl-phthalamide

N-{2-[4-(3,5-Dimethyl-isoxazole-4-sulfonyl)-piperazin-1-yl]-ethyl)-*N,N'*-bis-[2-(1*H*-indol-3-yl)-ethyl]-*N'*-methyl-phthalamide

N-(2-{4-[*N*-(2-*tert*-Butyl-phenyl)-*N'*-furan-2-ylmethyl-carbamimidoyl]-piperazin-1-yl}-ethyl)-*N,N'*-bis-[2-(1*H*-indol-3-yl)-ethyl]-*N'*-methyl-phthalamide, acetic acid salt

N-(2-{4-[*N*-Furan-2-ylmethyl-*N'*-(2-methylsulfanyl-ethyl)-carbamimidoyl]-piperazin-1-yl}-ethyl)-*N,N'*-bis-[2-(1*H*-indol-3-yl)-ethyl]-*N'*-methyl-phthalamide, acetic acid salt

N-(2-Benzo[*b*]thiophen-3-yl-ethyl)-*N'*-[2-(4-benzyl-piperazin-1-yl)-ethyl]-*N'*-[2-(1*H*-indol-3-yl)-ethyl]-*N*-methyl-phthalamide

N-[2-(4-Benzyl-piperazin-1-yl)-ethyl]-*N*-[2-(1*H*-indol-3-yl)-ethyl]-*N'*-methyl-*N'*-[2-(4-nitro-phenyl)-ethyl]-phthalamide

N-[2-(4-Benzyl-piperazin-1-yl)-ethyl]-*N'*-(2-biphenyl-4-yl-ethyl)-*N*-[2-(1*H*-indol-3-yl)-ethyl]-*N'*-methyl-phthalamide

15. Pharmaceutical compositions containing as active principle compounds according to any one of claims from 1 to 14.

16. Use of compounds according to any one of claims 1 to 14 for the preparation of pharmaceutical compositions suitable for the treatment of diseases in which tachykinin receptors are implicated.

17. Use of compounds according to claim 16 for the preparation of pharmaceutical compositions suitable for the treatment of diseases in which the use of tachykinin antagonists is indicated.

18. Use of compounds according to claim 17 for the preparation of pharmaceutical compositions suitable for the treatment of diseases in which the use of NK2 antagonists is indicated.

19. Use of compounds according to claim 18 for the preparation of pharmaceutical compositions suitable for the treatment of the bronchospastic component of asthma, cough, pulmonary irritations, intestinal spasms in general, Crohn's disease, ulcerous colitis, the irritable-colon syndrome, local spasms of the bladder and of the ureter during cystitis, and renal infections and colics.